Thesis for the Degree of M.D.

THE INFLUENCE OF THE VAGUS ON THE HEART RATE IN HEALTH AND IN CERTAIN PATHOLOGICAL CONDITIONS PARTICULARLY CARDIAC DISEASE.

by

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INTRODUCTION.

The effect of stimulating the peripheral vagus on the heart was discovered by Weber in 1846. Since then the action of this nerve on the heart has proved a fascinating study for physiologists. Most of the work done has been however of the nature of acute experiments in the laboratory. A few observations have been made in some particular disease, but apart from those there is no evidence in the literature that any systematic study has been made on the human heart showing the vagal effect at different ages and in different diseases, especially those known to cause permanent or temporary damage to the heart.

The importance of the influence of the vagus on the heart rate, as shown by the atropine test, came into great prominence during the War as the result of the admirable work of Marris on Typhoid Fever[57]. He showed that in this condition the vagal effect was much reduced. During the last 18 months I have spent considerable time in investigating the influence of the vagus on the heart rate in the normal heart at different ages, and also in patients suffering from various diseases. The results of this research are embodied in the thesis.

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The pathological conditions dealt with are principally those which are known to cause either permanent or temporary damage to the heart.

Muller[64] in 1891 carried out investigations along similar though less extensive lines. The results he obtained were so extremely interesting that it seemed desirable, in view of the great strides made in the study of heart disease and physiology since Muller's publication, to investigate the problem more completely and also to extend the scope of the inquiry in order that if variations in vagal effect did occur one might be able to correlate the results and arrive at a possible explanation of their causation.

As a preliminary to giving the result of my own researches a brief account of the Anatomy of the Vagus and a resumé of the present state of knowledge regarding the influence of the vagus on the heart rate are given in order to explain if possible the variations along physiological lines.

To make the results as complete as possible all the published cases in which the atropine test has been carried out in various diseases are included. Those borrowed from the publications of other authors have been noted.

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I wish to thank Prof. Cushny and Prof. Meakins for their help in suggesting various lines along which to pursue the investigation, and Prof. Meakins, Prof. Gulland, Dr Edwin Matthew and others in the Royal Infirmary for placing the patients under their charge at my disposal in order to carry out the research.

ANATOMY OF THE CARDIO-INHIBITORY MECHANISM.

A brief account is given of the anatomy in order that one may be able to see the points at which any interruption of the normal action may take place.

In his original communication Weber[78] localised the centre to the spinal bulb in the region between the cerebellum and the tip of the calamus scriptorius. Laborde[45] investigated this question in the cat and came to the conclusion that the centre was situated in the lateral part of the 4th ventricle some distance cephalad to the dorsal vagal nucleus - in the nucleus ambiguus. More recently Gehucter & Molhan[32] from histological evidence consider the centre to be in the dorsal vagal nucleus. On stimulating the medulla electrically Miller & Bowman[62] found that the centre was in the dorsal vagal nucleus and got no effect outside this except in the inferior fovea where the effect was much less and probably communicated.

The fibres leave the medulla in the groove between the olive and restiform body, and pass through the jugular foramen in the same sheath as the accessory nerve. In this situation there is a ganglionic/

ganglionic enlargement - the ganglion of the root. After leaving the jugular foramen it is joined by the cerebral portion of the accessory and another enlargement is found - the ganglion of the trunk. The vagus then descends in the carotid sheath and on the right side, enters the thorax by crossing the subclavian artery and descends along the side of the trachea to the back of the root of the lung. On the left side it enters the thorax between the carotid and subclavian arteries and crosses the left side of the arch of the aorta, and continues its course behind the root of the lung.

The cardiac branches are given off from the main nerve at various points. The Superior Cardiac Branches are given off at the upper and lower parts of the neck. Those from the upper part pass to the deep part of the cardiac plexus while the lower run on the right side to the deep part of the plexus and on the left side to the superficial part of the plexus. The Inferior Cardiac branches arise on the right side from the main trunk at the side of the trachea and also from the recurrent nerve, while on the left side they come from the recurrent nerve only. On both sides they pass to the deep part of the Cardiac Plexus.

The Cardiac Plexus is divided into a superficial and/

and deep part. It contains fibres from both the vagus and sympathetic. The superficial part lies beneath the arch of the aorta in front of the right pulmonary artery. The deep part is situated in front of the bifurcation of the trachea above the point of division of the pulmonary artery. There is also a posterior coronary plexus which runs with the left coronary artery and derives its filaments chiefly from the left half of the deep part of the cardiac plexus. An anterior coronary plexus is also found running with the right coronary artery.

In the heart itself are situated collections of ganglion cells with which the vagal fibres communicate. Where the fibres of the vagus enter the heart along the Superior Vena Cava there is a collection of cells - Remak's ganglia. In connection with the two vagus nerves in their course along the auricular septum we find Ludwig's ganglia and finally the vagus nerves terminate in the two ganglia at the A.V. junction known as Bidder's ganglia. A few ganglion cells have been found by Dogiel[19] and others in the ventricular tissue and along the nerve fibres passing from the sinus to the auricles. The main mass of the auricular and ventricular muscle as well as that of the bulbus arteriosus is free from cells.

The cardiac ganglia have been shown by His junior/

junior[38] to be found in connection with the vagus nerve as offshoots from the vagus ganglia, at first outside the forming heart and afterwards become included in the heart itself. He was of opinion that in man some of the cardiac ganglia were derived from the sympathetic. Kuntz[44] and Abel[1] while supporting the former statement both came to the conclusion that the ganglionic cells in the heart are only connected with the inhibitory mechanism.

The fibres of the vagus to the heart are medullated till they reach the cardiac ganglia and were shown by Gaskell to have no connection with the other ganglia on the vagus trunk. It is stated by Dogiel[19] that the individual fibres in the heart give off collaterals to various groups of cells before they terminate in arborisation around a final group of cells.

The post-ganglionic fibres of the vagus arise from the cardiac ganglion cells and are distributed to the cardiac muscle. These fibres are non-medullated.

Lewis[51] states that the intensive actions of the vagus are exerted on the specialised tissues of the heart. Rothberger and Winterberg[82] found that the right nerve had more effect on the sino-auricular node while the left had more effect on the auriculo-ventricular/

ventricular node. The sino-auricular effect has been abundantly confirmed in animals and Robinson and Draper[67] and Ritchie[66] found in the human heart comparable results to Rothberger and Winterberg. Lewis and Cohn[48] while agreeing with the former statement, found that both nerves acted equally on the auriculo-ventricular node.

The vagus has a direct though slight effect on the mammalian ventricle. This was demonstrated by Gaskell[30] but MacWilliam and Gaskell[30] showed that in Chelonia and Reptilia there was no action on the ventricle. According to the researches of Fredricq[27] most of the vagal fibres to the ventricle pass through the A.V. bundle.

EFFECT ON THE HEART RATE OF DIRECT STIMULATION OF THE VAGUS.

It is by this means that all the fundamental facts of the action of the Vagus on the heart have been found out. In 1846 Weber[78] published his remarkable discovery that stimulation of the peripheral vagus arrested the heart. This was soon abundantly confirmed. These experiments were carried out on the frog and as the vagus is a mixed inhibitory and accelerator nerve in this animal, accelerator effects were mixed up with inhibitory to some extent. On this account there raged a great controversy over the correct interpretation of the function of the vagus. However Gaskell[29] showed that pure inhibitory effects without accelerator contamination could be obtained in the frog by stimulation of the intracranial vagus. He demonstrated that the strength of current required to produce the effect was less than when the mixed nerve was stimulated and that the standstill lasted a much longer time. Gaskell also found that vagus arrest only occurs in the frog when the heart is well nourished.

If vagal stimulation is prolonged escaped beats occur which are much slower than normal. These escaped/

escaped beats are confined to the ventricle. They are favoured by distension of the heart cavities and are often synchronous with asphyxial gasps which supervene as the result of lack of blood supply to the respiratory centre.

Rothberger and Winterberg[82] found in animals that the right nerve had a greater effect on rate than the left. Robinson and Draper[67] also found this in the human heart. These results were confirmed by Ritchie[66].

Sustchinsky[77] stated that vagus stimulation had more effect after section of the accelerators. Hunt[40] in his excellent paper on the accelerator action on the heart confirmed this. The latter also found that whether the accelerator was stimulated during vagal stimulation or the vagus during accelerator stimulation or both simultaneously either for a short or a long period, the effect is determined by the relative strength of stimulation applied to the two nerves. The result in all cases of simultaneous stimulation is the algebraic sum of the results of separate stimulation with slight preponderance of the vagus.

Stewart[73] studied the influence of temperature on the cardio-inhibitory action. Most of his experiments/

experiments were on frogs. The heart was excised and the temperature of the solutions in which the heart was immersed was altered. He found that the initiation of inhibition is more difficult when the heart is cooled, but that cooling is more favourable to the continuance of the inhibitory action. When the temperature is raised the opposite effect is seen. Stewart also made a few experiments on the tortoise and found that for a considerable range above and below normal temperature it may be difficult to show any marked difference.. It is by no means easy to show that the minimal strength of stimulus needed to produce the inhibitory effect increases as the temperature falls and decreases as it rises.

Schiff[70] had previously stated that in the rabbit the vagus loses its action when the heart is heated and regains it when it is cooled.

Martin[60] repeating Stewart's experiments was unable to confirm Stewart's results as he got less effect when the temperature of the heart was high than when it was low. In his reply to Martin Stewart[75] states that what Martin shows is that the heart escapes more readily when the heart is at a higher temperature. Stewart however in this paper admits that animals probably vary greatly in this matter.

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The only experiments I know which have been performed on carnivorae are those of Baxt[8] who in dogs could find no difference in vagal effect whether the heart was heated, cooled or at the normal temperature.

Stewart[74] has also investigated the effect of partial section of the nerve. When one vagus is stimulated and partial section made of the nerve, increasing successively in depth, peripheral to the electrodes, evidence is shown that up to a certain point excitation with the same strength of current produces the same effect on the heart whether all the cardio-inhibitory fibres are stimulated or only a certain number. Beyond this point the effect is diminished but can be made as great by increasing the strength of stimulus. Beyond this again no increase in the strength of stimulus will produce any effect. When a relatively small number of inhibitory fibres is excited the heart may stop as promptly but recovers more rapidly.

ALTERATIONS IN HEART RATE DUE TO VAGAL EFFECT ON CONDUCTION.

The first work on the vagal effect on conduction was carried out by Gaskell[29]. Using the land tortoise and stimulating the vagus trunk he found that the rate in the auricle and ventricle was considerably reduced, while the rate in the sinus remained the same. This slowing was due to partial sino-auricular block. There is however no anatomical or physiological basis for assuming that such a condition is possible in man, although certain tracings have been published in which from the form of disturbance which is of the nature of intermissions one might imagine that sino-auricular block was present.

Gaskell also showed that in the suspended frog's heart a 2-1 block could be brought about at the A - V junction by vagal stimulation. This depressant effect was confirmed by Bayliss and Starling[10].

Since the introduction of electro-cardiography considerable advance has been made in the study of vagal action on conduction. Dale and Mines[17] showed by this means that stimulation of the vagus increased the resistance to the passage of impulses from the auricle to the ventricle and shortens the duration of electrical disturbance. Mines[63] by applying atropine to/

to the sinus eliminated the action of the vagus on the pace maker while retaining that on the A.V. junction and ventricle. In these experiments the rate of transmission from the auricle to the ventricle was decreased and the duration of excitability was diminished.

Rothberger and Winterberg[82] stated that the left nerve had a greater effect in producing this depression of A.V. conduction, and Robinson and Draper[67] and Ritchie[66] from their studies on the human heart also put forward this view.

Lewis and Cohn[48] state that both nerves are equal and that the supposed preponderance of the left nerve is more apparent than real as it is better seen when the sino-auricular rate is unaffected - a complication more likely to occur when the right is stimulated.

Lewis[49] has shown that the most susceptible region lies at the junction between the A.V. node and the auricular tissue because, when the auricle and ventricle are responding simultaneously to impulses from the A.V. node, not the S.A. node, on vagal stimulation conduction in the auricle suffers more than does that in the ventricle.

Partial heart block has often been demonstrated to be due to vagal action as it has been removed by/

by atropine. This vagus action of inducing a delayed transmission of impulses is more likely to occur when there is already present a tendency to heart block. Lewis[51] is of opinion that permanent high degree of heart block is probably never due to vagal action unless the vagus has been stimulated by drugs.

PHYSIOLOGY OF THE CARDIO-INHIBITORY CENTRE.

It is a well known fact which can easily be demonstrated by experiment that the vagi exert a tonic influence on the heart. These tonic impulses arise in the cardio-inhibitory centre. According to Soltmann[71] vagal tone is absent in the new born animal. Engstrom[22] however found that pressure on the head of the new born child slows the heart and this presumably acts through the vagus centre.

The tonicity of the centre can be altered by stimulation of afferent nerves, by alterations in arterial pressure and by psychic and emotional conditions. Bernstein[11] states that there is no tonicity of the centre as shown by increase in heart rate on section of the vagi if the section is preceded by section of the spinal cord. This has been disproved by Dubois[21]. Stewart and Pike[76] came to the conclusion that this centre was the least automatic centre and most dependent on afferent impulses. It regains its power of being affected by reflex stimuli before its tone. It is less easily resuscitated than either the respiratory or vaso-motor centres.

Hunt[40] believes that activity of the centre is more easily depressed when influences are at work which/

which of themselves tend to weaken its activity, e.g. if both vagi are intact stimulation of a sensory nerve may have no effect on the heart rate, but if one vagus is cut, although this in itself may not increase the rate, stimulation of a sensory nerve may then cause acceleration. He states that increased central efficiency increases the tonicity and that in order to obtain reflex acceleration the centre must be in an unstable state. If the heart is slow sensory stimulation quickens it, but if the heart is rapid slowing is produced. Hunt considers that in a mixed nerve there are two sets of fibres acting on the cardio-inhibitory centre - one causing stimulation and the other inhibition - and that the inhibitory regenerates more rapidly. These fibres have no relation to the vaso-constrictor or vaso-dilator fibres. The slowing which is found after section of the accelerators is in part due to vagal tone.

Aducco[2] states that starvation increases the excitability of the centre and respiratory arrhythmia becomes very marked.

Henderson[34] thinks that CO_2 is the normal stimulus for the cardio-inhibitory centre, but Dale and Evans'[18] results show this to be unlikely. Starling[30] states that asphyxia in the first and second/

second stages stimulates the centre.

Various drugs, e.g. morphia and digitalis have a stimulating action on the centre.

Hunt[40] states that Ether, Chloroform, large doses of Curara, loss of blood and severe operations diminish vagal tone.

CARDIAC REFLEXES.

This is one of the most fascinating fields in the physiology of the heart. The following are a few of the many questions which arise in this connection. Does the central tonus of the vagus depend on constant afferent impulses or does the centre possess automatism? What part does the vagus play in maintaining the normal heart rate and what is its share in the changes of rate which occur? Do these changes occur as a pure reflex or are they due to the dissemination of impulses from other parts of the brain? When the heart is beating slowly or rapidly what is the condition of activity of the vagus centre?

Bernstein[11] was one of the first to enter this field. He found that after section of the spinal cord, cutting the vagi produced no increase in rate. The operative procedures in this experiment caused considerable alteration in blood pressure and Dubois[21] has shown that, if the blood pressure remains about 9 to 10 cm. of Hg, section of the vagi gives the usual rise while if the pressure is below this it is much more difficult to produce.

As it is possible that the results described later may have their explanation in the upset of some of these reflexes, the work of subsequent investigators is somewhat fully described.

REFLEXES FROM THE HEART ITSELF.

The heart has afferent nerves but these do not convey sensations of touch and pain as was shown by Harvey's experiment on Viscount Montgomery.
Goltz stimulated these nerves and found that general reflex movements were produced. Francois-Franck[25] produced reflex inhibition of respiration by chemical stimulation of the inner wall of the heart.
Woolridge[79] stimulated the central nerves running superficially on the anterior wall of the heart and found.- (1) Slow rate and rise of arterial pressure or (2) Slow rate followed by acceleration and fall in arterial pressure. On stimulating those running on the posterior wall he got (1) Acceleration of rate or (2) Slowing of rate and fall in arterial pressure or (3) Rise in arterial pressure or (4) Fall in arterial pressure.

Gaskell[30] states that it is possible that the nerves on the inner wall of the heart may be stimulated by intra-cardiac pressure and thus the centre either excited or depressed. The heart would then control its own rate.

Knoll[42] found that compression of the heart with the fingers or by inflating the pericardium caused acceleration due to loss of vagal tone.

Bainbridge[6]/

Bainbridge[6] carried out a series of observations on the effect of increased venous filling of the right heart on the heart rate. He got acceleration of the heart whether the increased filling was produced by the rapid injection of a small amount of fluid or the slow injection of a large amount. He considers this to be reflex as it did not occur after section of the vagi and accelerators and ligature of the suprarenal veins. He says the effect is principally due to loss of vagal tone but that a small part is due to increased accelerator tone. The effect is not accompanied by changes in arterial pressure or respiration and does not depend on the character of the injected fluid. The acceleration begins as soon as the diastolic pressure is raised.

Sassa and Migazaki[69] confirmed the last observations. They state that the acceleration varies with the vagal tone and that in the frog and rabbit, which have no vagal tone, there is no acceleration. Reflex accelerator stimulation was only obtained in large dogs. They find that the effect can be produced by impulses from both auricles and great veins near the heart, but not from any peripheral vein. Thus they conclude that the afferent impulses pass in the vagi.

REFLEXES DUE TO CHANGES IN BLOOD PRESSURE.

v. Bezold[12] found on stimulating the central end of one vagus that the heart was slowed reflexly if the other vagus was intact. This may be accompanied by a rise or fall in arterial pressure according as the pressor or depressor fibres are the more powerful. He thinks that the arterial pressure may reflexly excite the cardiac centre in the bulb by way of these afferent fibres in the vagus.

Bainbridge[5] is of opinion that in no case does stimulation of the central end of one vagus slow the heart by diminution of accelerator tone.

Ludwig and Cyon[53] showed that stimulation of the Depressor nerve caused a slight slowing of the pulse with a marked fall in arterial pressure. This slowing was abolished by section of the vagi. Marey[56] states that if the cardiac nerves are intact a rise of arterial pressure always slows the heart and a fall accelerates it.

Francois-Franck[24] found that after division of the spinal cord injection of blood at high pressure into the peripheral end of the carotid artery slows the heart. Sudden anaemia produced by ligation of the carotid does the same, the centre being first stimulated and then depressed. Hill[37] suggested that with sudden expansion of the cerebral arteries, when/

when blood was forced into them, the bulb was compressed and thus rendered anaemic. Howell[39] finds however that there is no anaemia of the bulb as the cerebral venous outflow is not reduced. Stewart and Pike[76] consider that the stimulation in occlusion experiments is due to the high blood pressure in the rest of the body.

Eyster and Hooker[23] say that the slowing of the heart from raised blood pressure is due to two factors: (1) Direct effect on the cardio-inhibitory centre as shown by the above experiments. (2) Stimulation of the centre reflexly through afferent nerves. This is shown by the results obtained from the inflow of saline into the cardiac end of one or both carotids after ligature of the vertebral arteries, from ligature of the aorta with previous ligation of the cerebral vessels and from increasing the pressure in isolated portions of the aorta. They consider that the afferent path for this reflex has its origin to a great extent in the thoracic aorta. With few exceptions increased ventricular pressure caused no slowing. In some cases increased coronary pressure caused slowing but never to the same extent as increased aortic pressure. They obtained this slowing after section of the accelerator and depressor nerves and thus conclude that the afferent fibres run in the vagi. They also found that the reflex effect may be abolished while the direct remains. Starling[72] states that the afferent fibres run in the depressor nerve.

REFLEXES DUE TO STIMULI FROM THE RESPIRATORY MECHANISM.

The first research on this subject was performed by Hering[35] who found that by moderate expansion of the lungs the heart is accelerated. He stated that the afferent fibres for this reflex run in the vagi. Francois-Franck[25] stimulated the various parts of the respiratory tract and obtained slowing of the heart from stimulation of the nasal branch of the 5th nerve, the central end of the superior laryngeal nerve, the mucous membrane of the larynx above the vocal cords and the mucous membrane of the lungs. No such effect was found to follow stimulation of the mucous membrane of the larynx below the cords. Brücke finds that stimulation of the nasal mucous membrane or the depressor nerve still produce slowing after section of the vagi and concludes that part of the slowing is due to diminished accelerator tone.

Brodie and Russell[14] came to the conclusion that the pulmonary were the most effective fibres in the vagus in producing reflex slowing of the heart on central stimulation. The cardiac were much less effective and those below the pulmonary still less.

The next observation of importance was that of Yandell Henderson[34] who stated that, in animals with the chest open, sudden excessive pulmonary ventilation could increase the heart rate up to cardiac tetanus.

He/

He regarded CO_2 as the normal stimulus for all the medullary centres. Parkinson[65] found that inhalation of oxygen caused slowing of the heart in man. He did not ascribe this to central action but to increased efficiency of the heart itself and to the fact that the necessary oxygen can be conveyed to the tissues by fewer beats. Bainbridge[7] was unable to confirm the results of Brodie and Russell but confirmed those of Henderson. He found no evidence to support the suggestion of Traube that impulses pass by irradiation from the respiratory to the cardio-inhibitory centre. In his opinion the acceleration during excessive pulmonary ventilation is due to a larger return of blood to the right side of the heart which according to his work mentioned above, would cause an acceleration. Recently Dale and Evans[18] have studied very carefully the effect of CO_2 on the cardio-vascular mechanism. They found that the changes in the actual heart rate were very small and were not constant. In their experiments the characteristic change was a rapid fall in arterial pressure when pure air was used to ventilate the lungs. The results obtained by Henderson can therefore be easily explained as the increase in heart rate which is known to accompany a fall in arterial pressure.

In/

In connection with stimuli from the respiratory mechanism we have the interesting phenomenon of Respiratory or Sinus Arrhythmia. It is well seen in children, especially about puberty and during convalescence from acute fevers. It is not conspicuous in the adult. With natural respiration expiration lengthens cycles while inspiration shortens them. The longest cycles appear where the intrathoracic pressure is highest, the shortest when it is lowest. Section of the vagi or administration of atropine abolishes it. It affects the whole heart and the electrocardiogram is normal.

REFLEXES DUE TO STIMULI FROM THE ABDOMEN.

Any stimulation of abdominal viscera usually causes slowing of the heart. Mayer and Pribram[61] showed that sudden distension of the stomach produced this effect while Goltz found that tapping the intestines had a similar action. Carlson however stated that hunger contractions in the stomach accelerated the heart and that the acceleration was proportional to the amplitude of the contraction.

Roy and Adami[68] stimulated the splanchnic nerves and came to the conclusion that this caused stimulation of both cardio-inhibitory and accelerator centres.

Usually/

Usually the accelerator stimulus is the stronger and there is a primary acceleration. Later however there is a slowing owing to the vagal stimulation lasting longer, and to the rise in arterial pressure stimulating the inhibitory centre. In some cases the inhibitory action may be stronger from the first.

REFLEXES DUE TO STIMULI FROM PERIPHERAL NERVES.

Central stimulation of any peripheral nerve usually produces acceleration. Asp[3] in two out of four experiments got acceleration on stimulating a sensory nerve after the vagi had been cut. As stated above, Roy and Adami[68] describe a primary acceleration which they think is due to stimulation of the accelerators. Bayliss[9] showed that stimulation of the depressor nerve after section of the vagi caused acceleration. Hunt[40] objects to these results as he thinks the acceleration occurs too rapidly for it to be due to stimulation of the accelerators. He considers all reflex acceleration as due to loss of vagal tone. The acceleration is greater he says wheh the accelerators are intact as their normal tone is added to the loss of vagal tone. Hooker[80] states that, after section of both vagi and keeping the heart at/

at its original rate by stimulating the peripheral vagus, reflex acceleration occurs on stimulating a sensory nerve. Bainbridge[5] brings forward very strong evidence that the reflex acceleration is mainly due to loss of vagal tone, but that part is due to accelerator stimulation. There is also a slight increase later, due to increased production of adrenalin.

Gallavardin, Dufont and Petzetakis[28] have demonstrated that the pulse can be slowed by ocular compression

REFLEXES DUE TO MUSCULAR EXERCISE.

In 1893 MacWilliam[55] showed that in animals which can keep up sustained effort the tonicity of the vagus is great. Hering[36] came to the conclusion that the acceleration after exercise was partly due to loss of vagal tone and partly to accelerator stimulation. Hunt[40] thinks it is all due to loss of vagal tone but Bainbridge[5] supports Hering's contention.

Gasser and Meek[31] find that the acceleration begins as early as the cardiac cycle after the initiation of the exercise. They consider it due to/

to loss of vagal tone as accelerator stimulation has a longer latent period. They show that the acceleration persists after removal of the stellate ganglia. The acceleration is markedly reduced by section of the vagi if asphyxia is excluded. After denervation of the heart during the first few days asphyxia is readily induced and causes an increased production of adrenalin which quickens the heart. They consider however that the latter factor does not alter the rate in the normal animal. Part of the increase they attribute to increased temperature of the blood and another small part to accelerator stimulation. Martin and Gruber[59] do not consider that any of the acceleration is due to rise of temperature.

Douglas Haldane and Henderson[20] found on Pikes Peak (14109 ft.) that as a general rule the resting pulse during the first few days was more rapid than normal and then the rate gradually fell but did not quite reach normal. The pulse rate on exercise was much more increased than normal for the amount of exercise, but as they got acclimatised the effect wore off.

IS REFLEX ACCELERATION DUE TO ASSOCIATED INNERVATION FROM THE CEREBRAL CORTEX?

Francois Franck and Pitres[26] using slightly anaesthetised dogs obtained variable results on cerebral stimulation - unaccompanied by epileptic fits - sometimes acceleration and sometimes slowing. These differences appeared not to depend on the site of stimulation but on the condition of excitability of the cortex and on the strength of current - a strong current usually produced slowing and a weak acceleration. Hunt[40] states that cerebral stimulation never causes acceleration after section of the vagi.

Johannson[41] was of opinion that the acceleration due to exercise was due to associated innervation from the motor cortex. Athanasin and Carvallo[4] however obtained no acceleration in paraplegics in whom powerful but ineffectual efforts towards movement were made. They conclude that the acceleration is reflex. Bowen[13] says it is partly reflex and partly cortical. Martin and Gruber[59] agree with Johannson. Krogh and Linhard[43] using the Bergoni apparatus for tetanising muscles found that in voluntary work the acceleration arises from cerebral impulses while in inducing work - e.g. by tetanising muscles - it is produced reflexly.

CLINICAL CONDITIONS DUE TO ALTERATIONS IN VAGAL TONE.

Several well recognised clinical conditions have been shown to be due to alterations in vagal activity. The proof, that this is so, is that they have been temporarily removed by the administration of atropine which paralyses the vagus.

(1) Sinus Arrhythmia - see Reflexes due to Respiratory Mechanism.

(2) Partial Heart Block (a) Sino-auricular
(b) Auriculo-ventricular

see Vagal effect on Conduction.

(3) Phasic Irregularity. This condition has been described by Lewis[47]. The whole heart periodically slows independent of respiration or other reason. The rapid and slow phases may be of equal duration. Slowing and subsequent acceleration is gradual. This condition is sometimes seen during convalescence from an acute fever, after digitalis, and as the heart slows after it has been accelerated by exercise.

(4) Prolonged slowing associated with a fall in blood pressure[50]. The periods of slowing are longer than in Phasic Irregularity and the intervals between the attacks are measured in days or months. The heart slows gradually and is accompanied by an independent fall of blood pressure. This is often accompanied/

accompanied by loss of consciousness.

(5) Bradycardia. Prolonged slow action of the heart is often due to excessive vagal action. The slow heart in Jaundice has been shown by Lewis to be vagal in origin.

(6) Laslett[46] reported a case of standstill of the whole heart for 4-8 seconds, which was relieved by atropine.

(7) A combination of these irregularities may take place.

SHORT CRITICAL REVIEW OF THE ABOVE LITERATURE.

It is unnecessary at this point to deal in detail with each paper, therefore a statement will be given of the conclusions formed from the perusal of this literature. The more important papers will be fully discussed in the appropriate section.

It is proved beyond doubt that the vagus exerts a powerful restraining influence on the heart and that stimulation of the nerve by any means slows the heart rate. There also seems to be no doubt that the action of the accelerator nerves is opposite to that of the inhibitory nerves. Gaskell's statement that the vagus has a marked depressant action on the conducting mechanism in the heart has been abundantly confirmed. It seems improbable however that complete block can be produced in the normal heart by excessive vagus action. All those who have investigated the action of the right and left nerves on different parts of the heart are agreed that the right acts more powerfully on the sino-auricular node, but there is still a great deal of doubt as to whether the left acts more powerfully than the right on the auriculo-ventricular node. Most observers state that this is so, but the criticism of Lewis seems justified that/

that the greater effect of the right on the auricular rate makes this more apparent than real. When a constant auricular rate is maintained the difference is much less marked. There is a tendency even then however for the left to preponderate slightly.

Regarding the influence of alterations of the temperature of the heart or sino-auricular node on the effect of vagal stimulation there is considerable divergence of opinion. Stewart is of opinion that they produce a marked difference in the frog. Others obtain exactly opposite results from Stewart. Stewart brings forward very few figures in support of his contention. He found difficulty in confirming his results on the tortoise and in a later paper says animals probably differ greatly in this respect. There is no evidence in the literature to show that in the carnivorae heat or cold, within limits which do not destroy the structure of the heart have any influence on the action of the vagus on the heart. As this question has an important bearing on one of the problems studied in the present investigation it will be fully discussed later.

There is no doubt that the cardio-inhibitory centre is in a state of tonic activity. Whether the centre possesses automatism or its tone is maintained by/

by constant afferent stimuli is not clear. The strongest support of the latter was the work of Bernstein who found no increase in heart rate on cutting the vagi after section of the spinal cord. Recently Dubois has shown that the result obtained was due to a fall in arterial pressure. However although tone may still be present in the centre after section of the spinal cord, this does not prove automatism as stimuli might still pass to the centre in nerves which have no connection with the spinal cord.
It seems definitely established that at any rate the tonicity of the centre can be profoundly altered by impulses from other parts of the body and also by alterations in arterial pressure. The carefully conducted experimental work of Bainbridge and Eyster and Hooker lends strong support to the view that the tonicity of the centre can be affected by stimuli from the heart and great vessels. Although Brodie and Russell came to the conclusion that the pulmonary fibres were the most powerful fibres in the vagus in producing reflex alteration in the tonicity of the cardio-inhibitory centre, the experiments of Bainbridge which were carried out with more attention to detail, especially regarding the origin of the fibres stimulated, show that their conclusion was probably incorrect. The work of Dale and Evans is much/

much more convincing than that of Henderson regarding the effect of excessive pulmonary ventilation on the cardio-inhibitory centre. They show that the results obtained by Henderson were due to a marked fall in arterial pressure which lowers the tone of the inhibitory centre and that CO_2 has little direct action on this centre.

All observers agree that central stimulation of most sensory nerves usually produces acceleration of the heart. The researches of Bainbridge and of Gasser and Meek on this problem and also on the acceleration due to muscular exercise provide strong evidence that this acceleration is not wholly due to loss of vagal tone as Hunt supposed, but that there is a small part due to accelerator stimulation and also to increased supra-renal activity. It is very difficult to decide whether the acceleration caused by muscular exercise is due to impulses arising in the cerebrum or to impulses from the periphery affecting the centre reflexly. The results obtained by the various investigators differ greatly.

Bainbridge in his monograph on the Physiology of Muscular Exercise (1919) concludes that the primary acceleration is due to loss of vagal tone and also partly to accelerator stimulation. The

continued/

continued acceleration he thinks is due to cerebral impulses acting on the inhibitory centre, to an increased number of impulses passing from the right heart and to increase in body temperature - the latter only playing a very small part. In this work Bainbridge does not appear to give the attention which they deserve to papers supporting the reflex view and the evidence appears to be too conflicting to make any positive assertion. As all observers are agreed that stimulation of most sensory nerves lessens vagal tone the probability is that both factors play a part although it is at present impossible to say which is the more powerful. Another factor to be considered during the continued acceleration is that chemical changes in the blood as the result of the muscular exercise may influence the inhibitory centre.

The general impression formed from reading the literature is that most of the facts regarding the effects of stimulation of the peripheral vagus have been established, but that there still remains a great deal to be done before the part played by the various factors which influence the tone of the cardio-inhibitory centre can be stated with certainty.

PROBLEMS TO BE STUDIED IN THE PRESENT INVESTIGATION.

Two methods of investigation have been employed in this research. Wherever possible clinical investigation has been carried out but when it was not possible to investigate a problem in man, experimental observations have been made on animals. In man the tonicity of the vagus has been estimated by studying the results obtained after the administration of atropine sulphate which paralyses the myo-neural junctions of the vagus.

The first problems considered are - What is the influence of the vagus on the heart rate in normal persons of various ages? Does the influence of the vagus on the heart rate differ in the two sexes? Does the influence of the vagus on the heart rate in normal individuals vary with the initial heart rate?

These problems were investigated by the administration of atropine to a large number of hospital patients just before their discharge from hospital. In every case the heart was proved to be normal as far as was clinically possible.

The next question dealt with is - What is the influence of the vagus on the heart rate when the heart is damaged either permanently or temporarily, or when its normal functioning is interfered with in any way?

The first type of case selected for consideration is Chronic Heart Disease as in this there is no doubt that the heart has been grossly damaged. During these observations the part played by the vagus in the slowing produced in Auricular Fibrillation under the influence of Digitalis was also studied. The next series of cases dealt with is cases of Exophthalmic Goitre in which disease, as is well known, the heart is one of the organs which is most prominently affected. Observations made on cases of Parenchymatous Goitre are inserted for comparison. To complete the series the results obtained in some fibrile conditions during convalescence are given. Those selected are known to affect the heart either permanently or temporarily. Rheumatic Fever and Chorea play such a prominent part in the aetiology of cardiac disease that they seemed to be particularly suitable for study. The other diseases selected were Pneumonia and Typhoid Fever as these are known to produce definite though usually temporary changes in the cardiac muscle .

The final problem considered is - Does the tonicity of the cardio-inhibitory centre increase when the heart is beating at an abnormally rapid rate in order to counteract this? Does the tonicity of the centre decrease when the heart is beating at a very slow rate?

Clinical/

Clinical investigation did not seem to be a suitable method of studying this problem as in normal patients the variations in heart rate when at rest are comparatively small and any alteration in tonicity which may occur will probably be very small.
In cases where the rate is abnormally rapid or slow it is impossible to obtain an uncomplicated experiment. The tonicity of the centre might be greatly altered but the primary cause of the alteration in rate might so complicate the results that an entirely wrong impression would be obtained of the tonicity of the centre. In animal experiment it is possible to exclude to a very great extent influences other than the alteration in rate and thus more reliable results will be obtained.

To complete the investigation an endeavour is made to correlate the results along physiological lines.

TECHNIQUE OF THE PRESENT INVESTIGATION.

All cases included as normals were patients just before discharge and were shown as far as was clinically possible to have normal hearts. A certain number of observations were made on students and these are also included in the normal groups. In no case was the test carried out in which the temperature was raised.

The drug used to paralyse the vagus was Atropine Sulphate which was administered hypodermically in doses varying with the body weight of the patient - 1.5 mg. being given per 50 kilos. The patient remained at rest in bed and in a large number of cases the changes were recorded by Mackenzie's polygraph - in irregular hearts this was always employed. In others the heart rate was counted at the apex by auscultation. Before the injection was given frequent readings were taken for five to ten minutes, and when the rate was practically constant the average of five readings at this rate was considered to be the normal rate. The injection was then given and readings made at five minute intervals for an hour.

Tables have been arranged showing the results in the various groups investigated. The rise is divided into three groups - Large = above 30 beats per minute, Medium/

Medium = 14-30 beats per minute, Small = under 14 beats per minute. The group into which a particular case falls has been decided by the actual increase in rate, not by the percentage increase, although both actual and percentage increases are included in the tables for comparison. Where there has been a preliminary fall, as is often seen after atropine administration, the second figure represents this fall. The results obtained by other observers have been included in the appropriate table to make the results as complete as possible. Where the observation has been taken from the works of another observer this fact is noted and the dose of atropine he administered is included in the column where the doses are recorded.

THE VAGUS EFFECT ON THE HEART RATE IN NORMAL PERSONS AT VARIOUS AGES.

The only published work where this has been studied was done by Müller[64]. His paper shows a certain amount of lack of system. In some age periods he records a large number of cases while in others the observations are very scanty while in one there are none at all. It was consequently decided to investigate this subject systematically and on a larger/

larger scale than had been done by Muller.

Table I gives the results of each individual case investigated in the normal groups. The periods included in each group are periods of ten years. No case has been included from 1-10 as from the few observations made it was found that children became so excited by an investigation being carried out on them and by the prick of the needle that the heart rate was greatly increased even without atropine and thus fallacious results would probably be obtained.

TABLE I.

TABLE I.

The Influence of the Vagus on the Normal Heart at different ages.

*

10 - 20

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max.rise.
	1.	10		X	Bronchitis	108,96,145			0.6	37	34	27
	2.	10	X		TB. Hip	87,80,150			0.9	63	72	20
M	3.	13	X		Scabies	92,142			1.0	50	54	25
	4.	15		X	Subacute Nephritis	80,74,126			0.9	46	57	25
	5.	16		X	Bazant's Disease		59,53,80		1.5	21	36	30
M	6.	16		X	Syphilis	62,58,98			1.0	36	58	42
M	7.	16		X	Syphilis	84,128			1.0	44	52	27
	8.	17		X	Dysmenorrhoea	95,80,130			1.5	35	37	25
	9.	17	X		Paroxysmal Haemoglobinuria	80,110			1.2	30	37	40
M	10.	17		X	Typhus	76,120			1.2	44	58	17
M	11.	17		X	Syphilis	76,72,124			1.2	48	63	31
	12.	18	X		TB. Hip	76,71,125			1.2	49	64	40
M	13	18	X		Syphilis	106,136			1.2	30	28	18
M	14.	18		X	Syphilis	76,72,114			1.0	38	50	31
M	15.	18		X	Chancroid	88,130			1.5	42	48	23
	16	19	X		Bronchitis	72,120			2.1	48	67	25
	17.	19		X	Pleurisy	70,125			1.8	55	78	35
	18.	19		X	Bronchitis	72,126			1.8	54	75	30
M	19.	19		X	Syphilis	80,112			1.0	32	40	37
	19a.					70,111			1.5	41	58	31
M	20	19	X		Syphilis		74,66,88		1.5	14	19	25

20 - 30

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max. rise.
1	20	X		Normal (Student)	80,136			1.5	56	70	35
2	20	X		"	64,144			1.7	80	125	15
3	20		X	"	70,125			2.1	55	78	35
4	20	X		"	71,152			2.1	81	113	30
5	20	X		"	72,128			1.6	56	78	30
6	20	X		"		72,68,96		1.9	24	33	24
7	20		X	"	72,126			1.8	54	75	30
8	21	X		"	72,124			2.1	52	73	30
9	21	X		"	65,112			1.6	47	72	35
10	21	X		"	76,120			1.7	44	58	25
11	21	X		"	72,121			2.1	49	68	35
12	21	X		"	72,124			1.7	52	73	35
13	21		X	"	78,132			2.2	54	69	38
14	21	X		"	70,124			1.9	54	75	30
15	21		X	"	72,164			1.6	92	128	25
16	21		X	"	68,132			1.5	64	94	30
17	21	X		"	78,108			2.3	30	38	20
18	21	X		"	72,108			1.8	36	50	33
19	21	X		"	76,128			1.9	52	68	40
20	21	X		Diabetes		64,60,91		1.6	27	42	18
M 21	21		X	Syphilis		80,74,108		1.5	28	35	26
M 22	21	X		Normal (Student)	86,128			1.5	42	49	25
M 23	21	X		"	62,60,128			1.2	66	107	15
M 24	21	X		"	68,100			1.5	32	47	26
M 25	21	X		"	90,88,128			2.0	38	42	36
M 26	21	X		"	70,108			1.5	38	54	53
M 27	21	X		"	70,66,112			1.5	42	60	46
M 28	21	X		"		68,50,82		1.5	14	21	37

20 - 30 (contd.)

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max.rise.
	29	22	X		Normal (Student)	78,72,120			1.6	42	54	35
	30	22	X		"	65,110			1.8	45	69	20
	31	22	X		"	83,124			2.1	41	49	50
	32	22	X		"	72,114			2.1	42	58	25
	33	22		X	"	74,125			1.9	51	69	15
	34	22	X		"	72,120			1.9	48	67	15
	35	22	X		"	72,102			1.9	30	41	25
	36	22	X		"	75,69,108			2.1	33	44	40
	37	22	X		"	66,108			2.1	42	64	35
	38	22	X		"		74,67,100		1.8	26	35	40
	39	22	X		"	84,126			1.7	42	50	25
	40	22	X		Hyperchlorhydria	78,72,120			1.5	42	54	35
	41	22	X		Constipation	72,102			2.0	30	41	25
	42	23	X		Normal (Student)	46,90			1.9	44	95	20
	43	23	X		"	64,118			1.9	54	84	35
	44	23	X		"	72,108			1.7	36	50	25
	45	23	X		Diabetes	66,120			2.0	54	82	25
M	46	23		X	Syphilis	94,92,128			1.2	34	36	21
	46a					84,128			2.0	44	52	35
	47	24	X		Normal (Student)	72,132			1.9	60	83	35
	48	24	X		"	64,110			1.5	46	72	35
	49	24	X		"	72,116			1.7	44	61	30
	50	24	X		"	66,108			1.7	42	64	36
	51	24	X		"	64,114			1.8	50	75	45
	52	24	X		"	78,72,108			1.7	30	39	33
	53	24	X		"	84,126			1.6	42	50	28
	54	24	X		"	78,63,128			1.9	50	64	35
	55	24	X		Constipation	70,112			2.0	42	60	25
M	56	24	X		Syphilis		66,64,90		2.0	24	36	34
	56a	24					66,60,82		1.0	16	24	61

20 - 30 (contd.)

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max. rise.
57	25	X		Normal (Student)	76,128			1.9	52	70	35
58	25	X		"		64,60,90		1.8	26	40	35
59	25		X	"	92,138			1.8	46	50	30
60	25	X		"	80,126			1.9	46	57	30
61	25	X		"	81,124			2.0	45	53	25
62	25		X	"	90,144			1.6	54	60	20
63	25	X		"	78,60,114			1.6	36	46	45
64	25	X		"	72,124			2.1	52	72	30
65	25	X		"	72,66,120			1.9	48	66	45
66	25	X		"	72,108			1.9	36	50	20
67	25	X		"	80,120			2.1	40	50	30
68	25	X		"	76,155			1.5	79	104	30
69	25		X	Gonorrhoea	88,73,140			1.6	52	59	25
70	25	X		Appendicitis	59,52,92			1.7	33	59	25
71	26		X	Normal (Student)	72,115			1.7	43	60	35
72	26	X		"	72,108			1.9	36	50	35
73	26	X		"	72,125			1.8	53	73	31
74	27	X		"	75,69,108			2.1	33	44	25
75	27	X		"	72,128			2.4	56	78	35
76	27	X		"	72,116			1.8	44	61	40
77	27	X		"	65,108			2.2	43	66	45
78	27		X	"	76,150			1.8	74	95	25
79	27	X		"	72,126			2.3	54	75	25
80	27	X		Hyperchlorhydria	75,69,108			2.1	33	44	25
M 81	27	X		Gonorrhoea		54,50,70		1.0	16	30	16
81a					58,52,88			1.5	30	52	6
M 82	27		X	Syphilis	70,114			1.0	44	63	36
83	28		X	Normal	76,144			1.6	68	90	30
84	29		X	Pyelitis	90,84,126			1.5	36	40	25
85	29		X	Renal Colic		74,62,96		1.6	22	30	35

30 - 40.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max. rise.
	1.	30		X	Anaemia		81,72,104		1.2	23	28	35
	2	30		X	Normal	72,106			1.6	34	47	35
	3	31		X	Debility	72,60,120			1.9	48	66	30
	4	33		X	Disseminated sclerosis.	66,126			1.4	60	90	25
	5	33	X		Renal Calculus		68,66,96		1.7	28	41	30
	6	34		X	Asthma	90,120			1.2	30	33	20
	7	34		X	Alcoholism	66,102			1.5	36	54	20
M	8	34		X	Hyperidrosis		68,96		1.0	28	41	23
	8a						70,64,96		1.5	26	37	36
	8b						76,71,104		2.0	28	37	36
	9	35		X	Constipation	86,78,138			1.6	52	60	30
M	10	35	X		Chronic Transverse Myelitis	56,50,92			2.0	36	64	61
M	11	35	X		Gonorrhoea		76,70,96		1.0	20	26	21
	11a						66,87		1.5	21	32	26
M	12	35		X	Hemiplegia		102,100,122		1.0	20	20	26
	13	37		X	Neurasthenia	73,62,156			2.0	83	114	30
	14	39		X	Achlorhydria	69,66,114			1.5	45	65	25
	15	39		X	Rheumatoid Arthritis.	90,120			1.2	30	33	15
	16	39	X		Normal		85,78,114		2.4	29	34	40
M	17	39	X		Debility	58,56,96			1.0	38	66	51

40 - 50.

No.	Age.	M.	F.	Disease	Large.	Medium.	Small	Dose	Rise	% Rise	Time of Max. rise
1	41	X		Encephalitis Lethargica.		90,107		2.0	17	19	12
2	42		X	Gastritis	66,126			1.3	60	90	20
3	43	X		Nephritis	75,106			1.5	31	41	25
4	43	X		Bronchitis		84,74,106		1.6	22	26	20
5	45	X		Emphysema	58,52,88			1.8	30	52	30
6	46	X		Duodenal Ulcer		81,78,107		1.8	26	32	25
7	46	X		Constipation		70,98		2.8	28	40	30
8	49	X		Duodenal ulcer.	51,96			1.8	44	88	25
9	49		X	Rheumatoid arthritis.		86,72,114		1.8	28	32	25
10	49	X		Debility	49,47,82			2.0	33	67	40

50 - 60.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose	Rise	% Rise	Time of Max. rise.
M	1	50.		X	Anaemia		86,102		1.0	16	19	31
M	2	50	X		Debility		76,72,94		1.0	18	23	61
	2a						68,62,88		1.5	20	30	36
	3	51		X	Hyperchlorhydria	69,102			2.6	33	48	15
M	4	51	X		Normal			61,52,70	1.0	9	15	40
	4a							64,60,74	2.0	10	16	14
	5	52		X	Gastric Carcinoma			91,102	1.5	11	12	15
	6	52		X	Gall Stones		70,92		1.8	22	30	30
	7	52		X	Ileal Kink		78,72,96		1.5	18	23	15
	8	53	X		Diabetes		83,72,110		1.7	27	32	40
M	9	53		X	Rheumatoid arthritis.		72,90		1.0	18	25	26
	9a						68,65,86		1.5	18	27	31
	10	55		X	Obesity		51,49,72		2.2	21	41	35
M	11	55	X		Normal		66,88		1.0	22	33	15
	12	56		X	Gastric Carcinoma	75,120			1.5	45	60	15
	13	56	X		Gastric Carcinoma	90,126			1.5	36	40	25
	14	56		X	Diabetes		62,84		1.4	22	35	15
M	15	58	X		Arterio Sclerosis			82,90	1.0	8.	9	39
	15a							69,65,80	2.0	11	16	34
	16	59	X		Epithelioma of tongue.	68,53,98			1.5	30	44	40

60 - 70.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Time of Max. rise.
	1	60		X	Arterio-sclerosis.	78,120			2.2	42	54	15
	2	60		X	Sciatica		76,72,105		1.7	29	38	40
M	3	60		X	Chronic Bronchitis			82,78,90	1.0	8	9	25
	3a							83,92	2.0	9	11	8
M	4	60		X	Hemiplegia		84,78,102		1.5	18	21	35
	5	61	X		Diabetes		80,75,95		1.5	15	19	35
M	6	62	X		Arterio-sclerosis			68,60,76	1.0	8	12	25
	6a					70,63,102			2.0	32	46	23
M	7	62	X		Normal		68,64,88		1.0	20	30	35
M	8	64	X		"		70,66,90		1.0	20	29	35
	8a						68,64,92		2.0	24	35	28
M	9	65	X		Kyphosis		82,98		1.0	16	20	40
I	9a							94,98	2.0	4	4	15
M	10	65	X		Emphysema			78,69,84	2.0	6	8	56
	10a						74,88		1.0	14	19	39
M	11	65		X	Arterio-sclerosis			92,105	1.0	13	14	14
	11a						80,94		2.0	14	17	10
M	12	65		X	Arterio-sclerosis		80,100		1.0	20	25	14
M	13	65		X	Arterio-sclerosis		78,94		1.0	16	20	15
	14	66		X	Debility	94,145			1.9	51	54	15
	15	66	X		Gastric Carcinoma			72,76	2.0	4	6	25
	16	66	X		Lymphadenoma		81,110		1.6	29	36	15
	17	67		X	Gastric Carcinoma	66,102			1.2	36	55	10
M	18	67		X	Debility		66,88		1.0	22	33	30
M	19	67	X		Debility		60,86		1.0	26	43	20
M	20	67		X	Debility		83,80,102		1.0	19	23	15
M	21	68		X	Debility			76,72,84	1.0	8	11	30
	21a							76,72,84	1.2	8	11	38
M	22	68	X		Fibrosis of Lungs		58,54,80		1.5	22	38	39
M	23	68	X		Debility		67,66,92		1.0	25	37	25
	24	69	X		Sciatica		67,96		1.6	29	43	30
	25	69		X	Rheumatoid Arthritis		66,90		1.7	24	37	20
	26	69	X		Arterio-sclerosis	67,106			1.4	39	58	30

- 70 -

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose	Rise	% Rise	Time of Max. rise.
	1	70	X		Chronic Nephritis		78,96		2.1	18	23	25
	2	70	X		Chronic Nephritis		77,67,92		2.0	15	19	25
M	3	70	X		Debility		72,98		1.0	26	36	23
M	4	70	X		Senile Kyphosis			60,70	1.0	10	16	13
	4a							59,55,64	2.0	5	8	33
M	5	70	X		Debility		60,58,79		1.0	19	31	25
M	6	71	X		Arterio-sclerosis	72,62,102			1.0	30	42	19
M	7	71	X		Debility		72,90		1.0	18	25	15
	7a							78,76,88	2.0	10	13	18
	8	74		X	Bronchitis	93,92,129			1.2	36	39	21
M	9	75	X		Tertiary Syphilis			82,80,89	1.0	7	9	31
	9a							80,90	2.0	10	12	42
M	10	75	X		Chronic Bronchitis			72,82	1.0	10	14	15
	10a							70,68,83	2.0	13	18	17
M	11	75		X	Senile Kyphosis		100,94,128		1.0	28	28	15
M	12	78		X	Debility		74,102		1.0	28	38	20
	13	80		X	Chronic Bronchitis			72,78	2.0	6	8	10
M	14	80	X		Debility	71,106			1.0	35	50	20
M	15	80		X	Debility		62,90		1.0	28	45	18
M	16	86	X		Emphysema			56,68	1.0	12	21	30
	16a						51,49,66		1.5	15	29	26

Figs. 1 - VII are curves of the reaction obtained after administration of atropine at each age period included in Table I. These curves have been obtained by adding the pulse rate of every case in the group at each five minutes after the administration and dividing by the number of cases in the group.

Fig. VIII shows these results plotted on one chart so that they may be more easily compared.

Fig. I. Effect of Vagal Release - 10-20.

Fig. II. Effect of Vagal Release - 20-30.

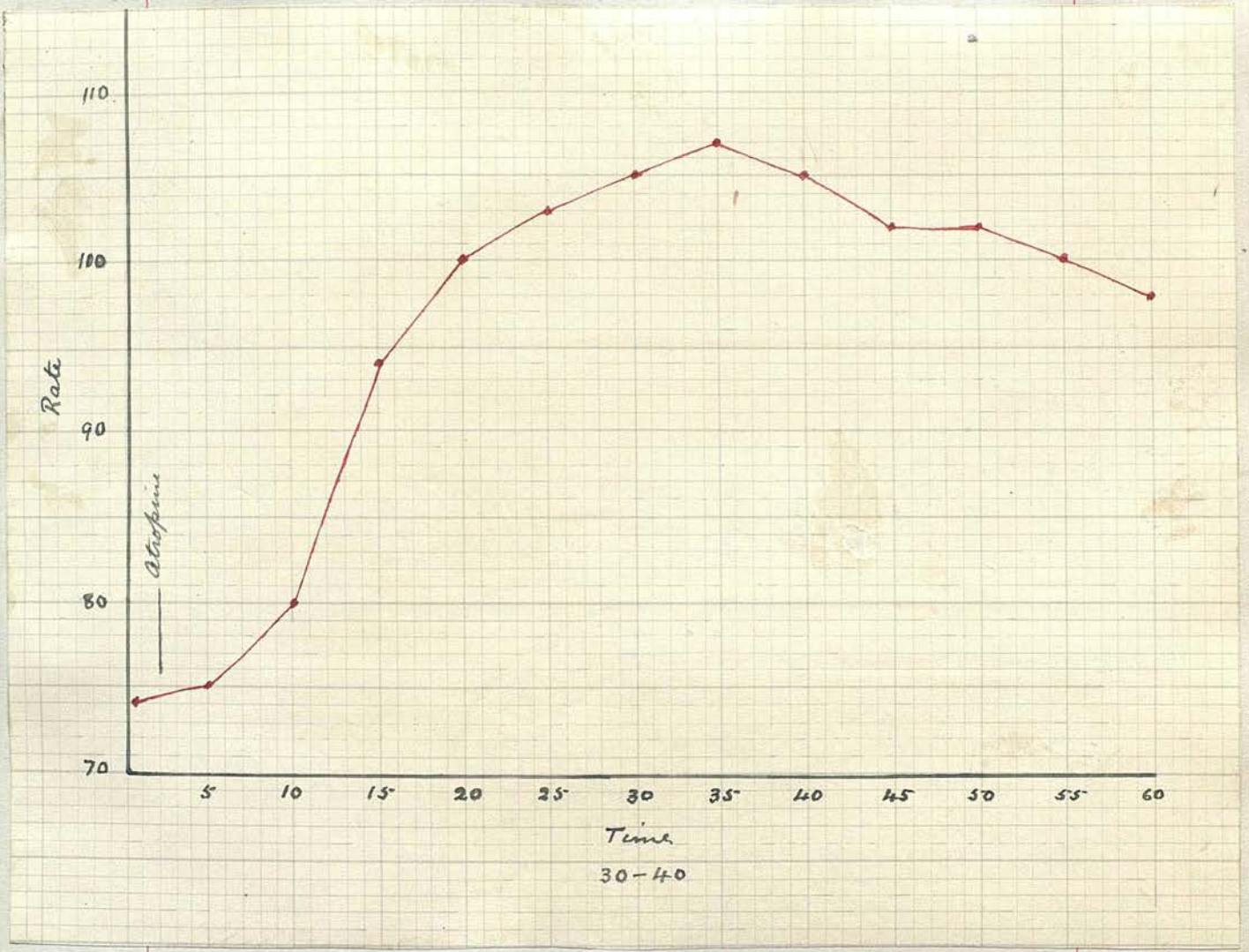

Fig. III. Effect of Vagal Release - 30-40.

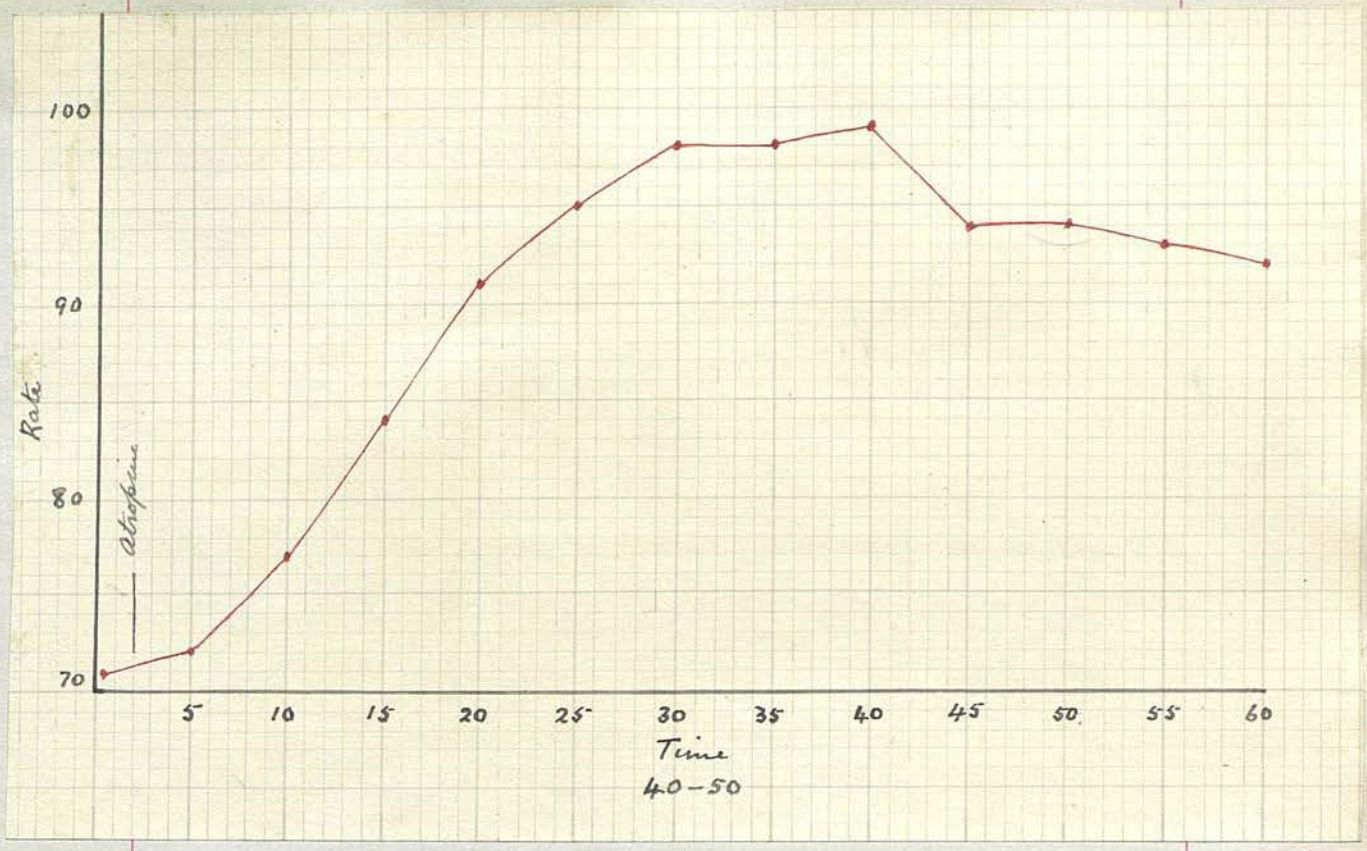

Fig. IV. Effect of Vagal Release - 40-50.

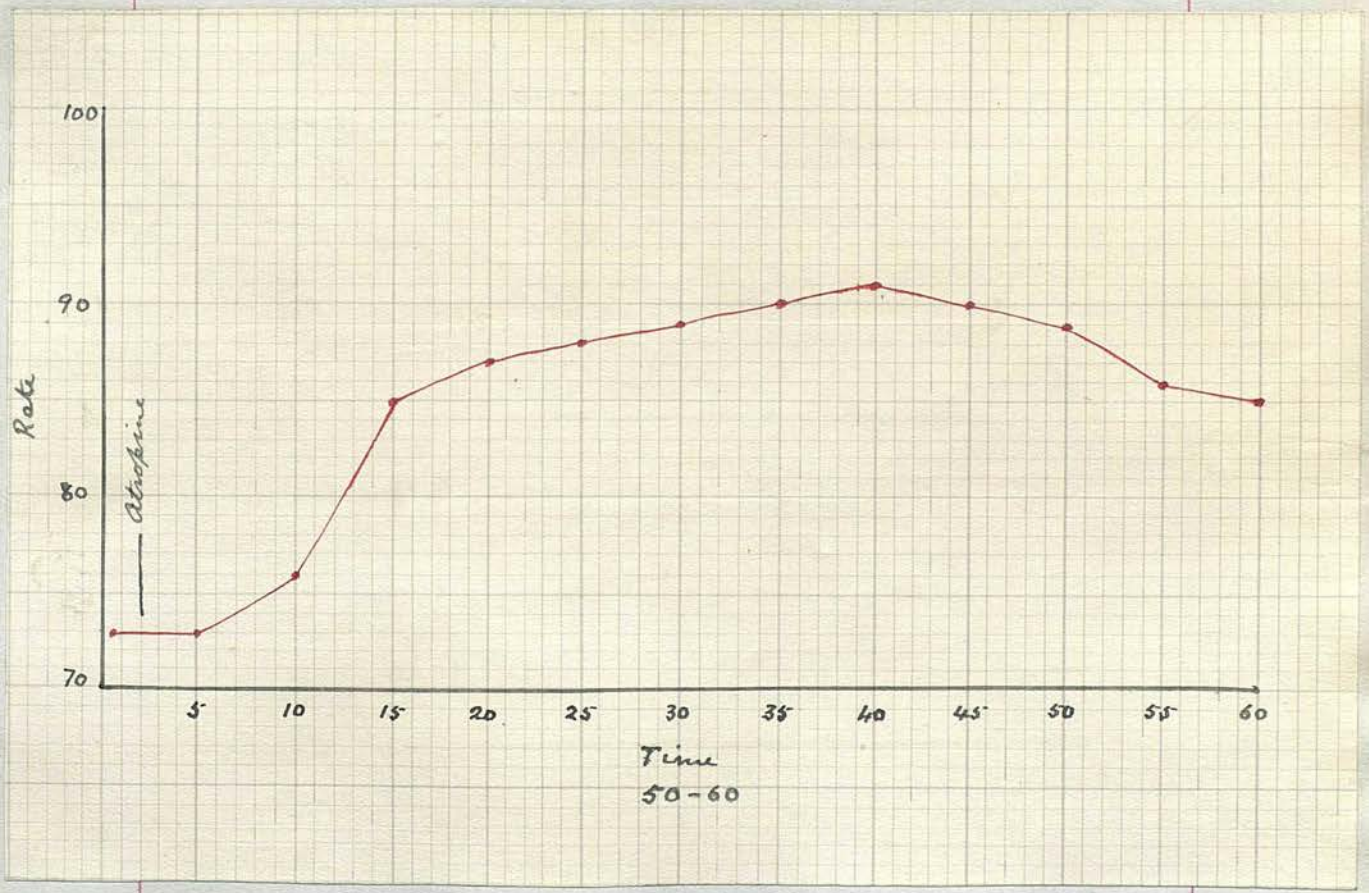

Fig. V. Effect of Vagal Release - 50-60.

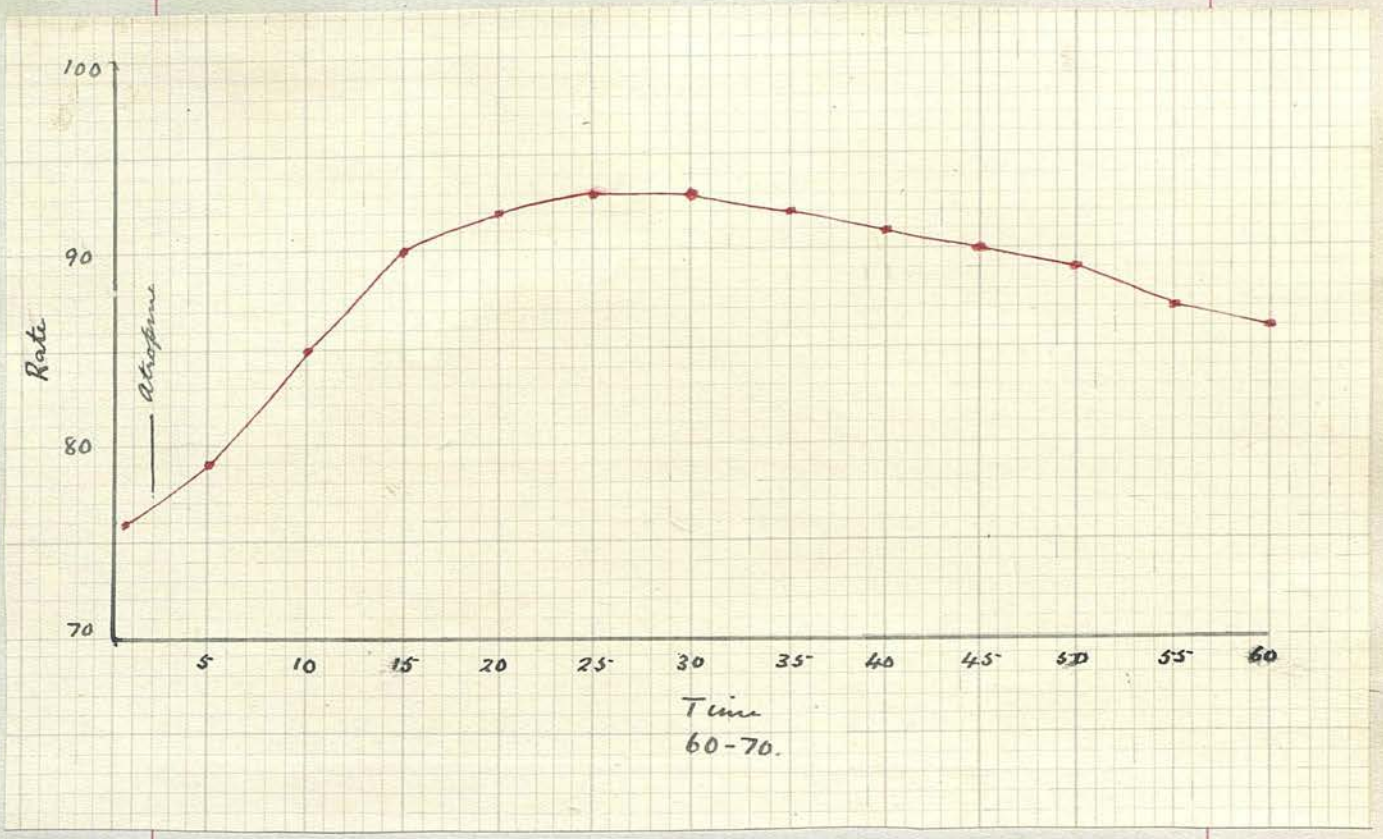

Fig. VI. Effect of Vagal Release - 60-70.

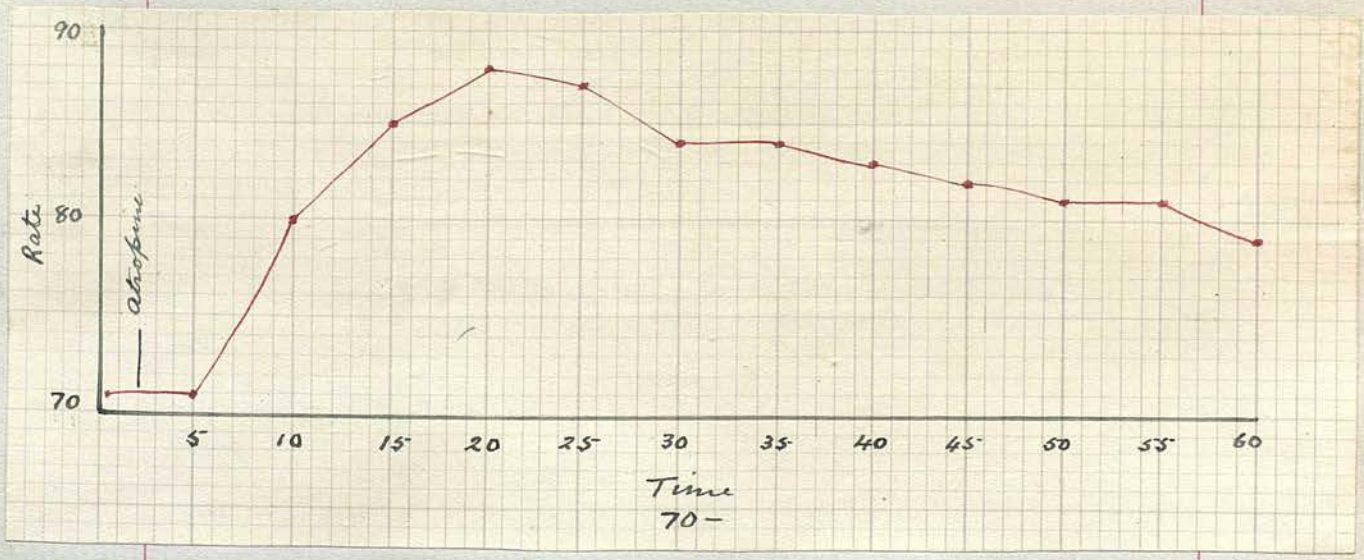

Fig. VII. Effect of Vagal Release - 70 -

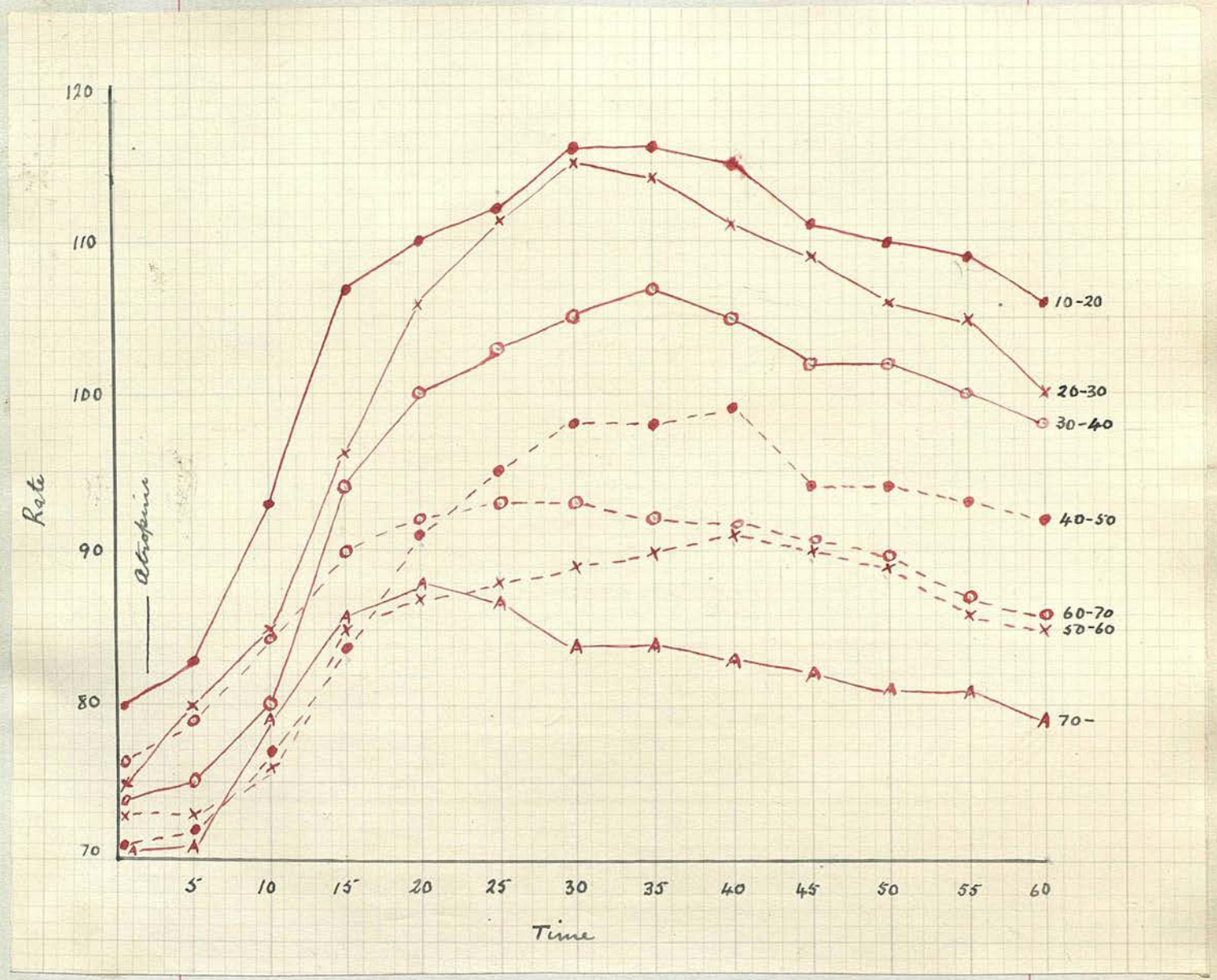

Fig. VIII. Effect of Vagal Release in the different Age Groups.

●—● 10-20, x—x 20-30, o—o 30-40, ●--● 40-50

x--x 50-60, o--o 60-70, a—a 70 -

Table II gives an analysis of the above cases. In this and similar tables where two observations have been made on any case within one or two days with no change in the condition of the patient the maximum increase obtained is used as representing the amount of vagal activity. The average is thus obtained by using only one observation on each case.

TABLE II.

Analysis of Cases at Various Ages.

Age.	No. of Cases.	Rise.	% Rise.
10-20	20	41.25	52.25
20-30	85	45.1	62.2
30-40	17	37.7	55.5
40-50	10	31.9	48.7
50-60	16	22.6	31.6
60-70	26	23.2	31.8
70 -	16	20.9	28.7

Fig. IX shows curves of the Actual Increase in Rate and the % Increase at the different age periods. It is seen that both curves are very similar although the Actual Rise is lower than the % Rise.

Fig. X shows curves of the Initial Rates and maximum reaction obtained in the various groups.

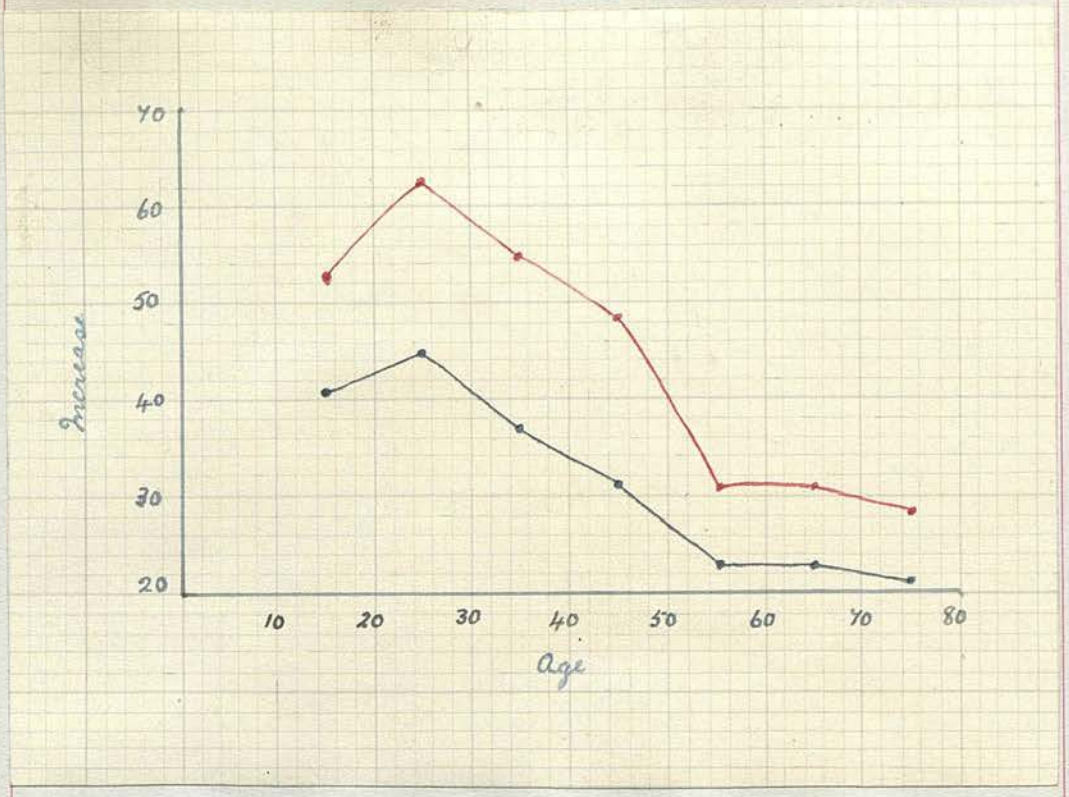

Fig. IX. Actual Increase and % Increase in Rate after Atropine at various Age Periods.
●——● Actual Increase. ●——● % Increase.

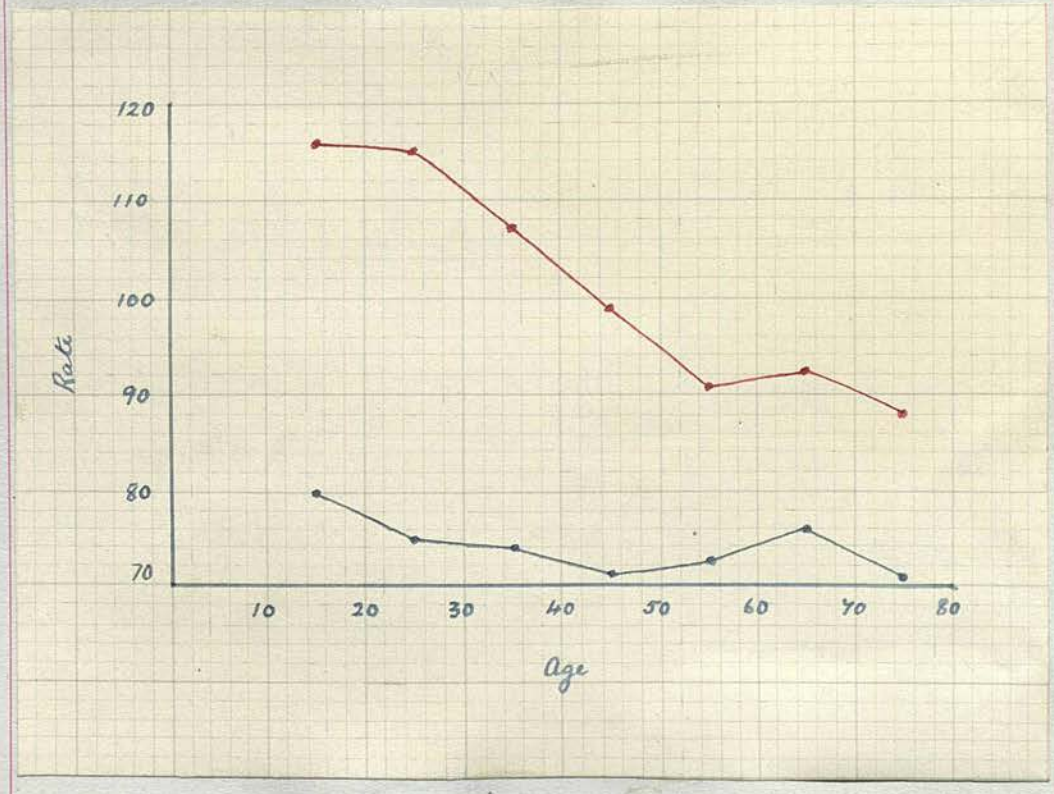

Fig. X. Original Rate and maximum height attained after Atropine at Various Age Periods.
●——● Original Rate. ●——● Maximum.

Summary of Results.

It is seen that the age incidence of maximum vagal activity is from 10-40. The period of greatest activity is between 20-30. After this the activity begins to diminish gradually, while after 50 the effect of atropine administration becomes much less marked.

Table I shows that there is considerable individual difference but when the average of the cases in each group is taken, a uniform curve is obtained throughout life.

Relation of Sex.

The results obtained showed no appreciable difference between the reaction in the two sexes.

Relation of Increase to Initial Rate.

Table I shows that cases which fall into the groups Medium and Small are by no means always the cases with the more rapid initial rates. The difference between the various groups in this respect is so slight that one may say that with normal heart rates one cannot judge what the actual rise is likely to be from the original rate. Naturally the % rise tends to be smaller in the cases with higher initial rates than it would be if the same rise were obtained/

obtained with a lower rate.

It is seen that the period of maximum release after subcutaneous injection of atropine occurs usually from 20-40 minutes after administration. There is in many cases a preliminary fall in rate such as has been previously described.

THE VAGUS EFFECT ON THE HEART RATE IN CHRONIC HEART DISEASE.

The only previous work on this problem forms the second part of Muller's[64] paper. These cases along with other published cases and my own cases are included in Table III. Some cases of Muller's in which he states Digitalis had been previously administered have been omitted as this introduces a complicating factor. Other cases, with an irregular pulse, which he classifies as Mitral Stenosis have been left out as these were probably cases of Auricular Fibrillation, which was unknown when his paper was published, and from the details it is impossible to allocate them to their proper group.

In their work on Auricular Fibrillation Cushny, Marris and Silberberg[16] publish a series of results of atropine administration in these cases not under Digitalis and these are also included as are three cases by Lewis in which the injection was subcutaneous.

TABLE III./

TABLE III.

The Influence of the Vagus on the Heart Rate in Chronic Heart Disease.

Aortic Disease.

	No.	Age.	M.	F.	Disease.	Large.	Medium	Small.	Dose.	Rise.	% Rise.	Remarks.
M	1	17	X		Aortic			82,76,84	1.5	2	2	
M	2	35	X		"			78,75,78	1.0	-	-	
M	3	40	X		"		80,102		1.0	22	27	
M	4	48	X		"			52,49,50	1.0	-	-	
	4a							40,42,45	1.0	5	12	
M	5	50	X		"			63,74	1.0	11	17	
	5a							70,64,75	1.5	5	7	
M	6	50	X		"			65,77	1.0	12	18	
	6a							80,76,90	1.0	10	12	
	6b						63,60,77		1.5	14	22	
	6c						68,65,91		2.0	23	34	
M	7	50		X	"			80,79,83	1.5	3	3	
M	8	54	X		"			88,90	1.5	2	2	
	9	55		X	"			79,90	1.2	11	14	
M	10	56		X	"			80,78,92	1.0	12	15	
	11	61	X		"			66,72	1.6	6	9	
	12	66	X		"		63,61,78		2.0	15	24	
M	13	71	X		"		78,68,100		1.0	22	28	
M	14	75		X	"		88,112		1.5	24	27	
M	15	93	X		"		76,102		1.2	26	34	

Mitral Insufficiency.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose.	Rise.	% Rise.	Remarks.
M	1	14	X		Mitral Insufficiency	64,122			0.5	58	90	
M	2	20	X		"	80,122			1.0	42	52	
M	3	37		X	"		126,140		1.0	14	11	
	3a							112,108,118	1.0	6	5	
M	4	40		X	"			48,60	1.0	12	25	
	4a						36,56		1.5	20	55	
M	5	41		X	"		120,138		1.5	18	15	
M	6	47		X	"			100-106	1.5	6	6	
M	7	66	X		"			96,92,108	1.0	12	12	
M	8	69		X	"			84,88	1.5	4	5	
M	9	70		X	"	92,123			1.5	31	33	

Mitral Stenosis.

	1	16		X	Mitral Stenosis.		135,150		1.4	15	11	
	2	27		X	"			87,84,93	1.5	6	7	
	3	46		X	"			76,67,87	1.6	11	14	

Non-Valvular Heart Disease.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose	Rise	% Rise	Remarks.
	1	31	X		Subacute Endocarditis			115,124	1.9	9	8	
	1a							116,125	1.9	9	8	
M	2	31		X	Dilatation		76,90		1.0	14	18	
C	3	35	X		Heart Failure		60,78		1.2	18	30	
	4	42		X	Multiple Extra Systoles			65,70	2.2	5	7	On admission.
	4a						63,61,78		2.0	15	24	Before discharge
M	5	42	X		? Coronary Sclerosis.			69,66,76	1.0	7	10	
	5a							80,86	2.0	6	7	
M	6	46	X		Hypertrophy & Dilatation.		62,76		1.0	14	22	
	7	50		X	Exophth. Goitre Aur. Fibrill.		106,120		1.5	14	13	
M	8	50		X	Hypertrophy & Dilatation.			90,102	1.2	12	13	
	8a							92,100	1.5	8	9	
M	9	54	X		Heart Failure & Emphysema	78,108			1.0	30	38	
	10	59	X		Multiple Extra-systoles.			96,96	2.1	-	-	
M	11	65		X	Dilatation		82,100		1.0	18	22	
C	12	66	X		Heart Failure			66,74	1.2	8	12	
M	13	70	X		Dilatation	100,98,140			1.0	40	40	
M	14	70		X	Dilatation		94,108		1.0	14	15	
M	15	80		X	Dilatation	82,127			1.0	45	55	

Auricular Fibrillation.

	No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose	Rise	% Rise	Remarks.
C	1	14	X		Auricular Fibrillation	120,160			1.2	40	33	Digitalis free.
C	2	17		X	"	120,173			1.2	53	44	"
C	3	24	X		"	81,135			1.2	54	67	"
C	4	27	X		"	87,135			1.2	48	55	"
C	5	35		X	"	100,144			1.2	44	44	"
C	6	35	X		"		75,95		1.2	20	27	"
C	7	42		X	"	125,185			1.2	60	48	"
C	8	45	X		"			105,115	1.2	10	9	"
C	9	50	X		"	108,154			1.2	46	42	"
C	10	67	X		"			120,126	1.2	6	5	"
L	11					115,165			1.2	50	43	"
L	12					100,170			1.8	70	70	"
L	13					90,140			1.2	50	55	"

M = Muller[64]
C = Cushny, Marris & Silberberg[16]
L = Lewis[52]

Fig. XI shows the type of reaction obtained throughout the period of observation in the various heart conditions studied. A normal curve of the age period corresponding to the average age of the heart cases is inserted for comparison.

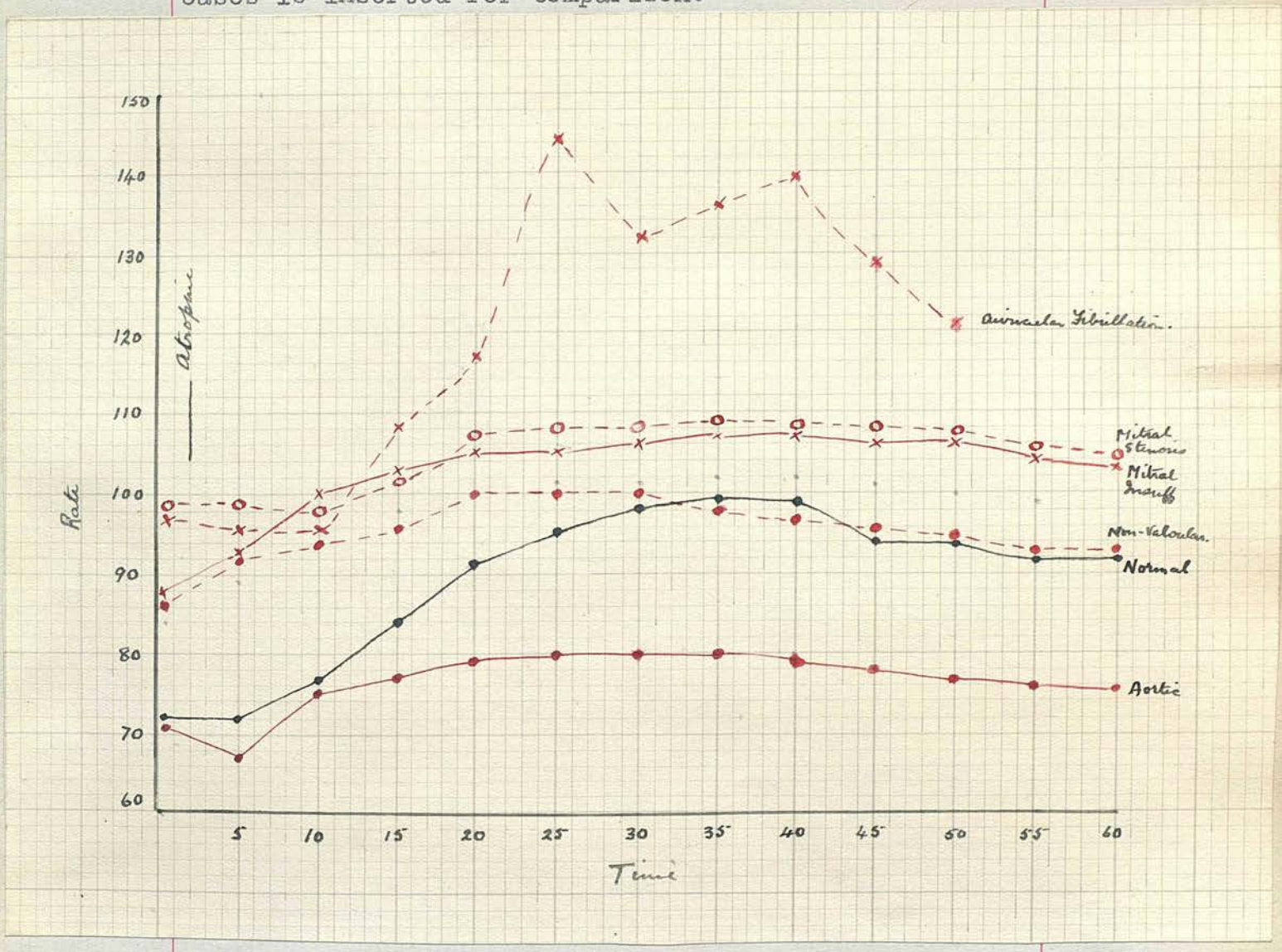

Fig. XI. Effect of Vagal Release in Chronic Heart Diseases compared to normal for same age period.

●—● Aortic. x—x Mitral Insufficiency
o--o Mitral Stenosis ●--● Non-valvular
x--x Auricular Fibrillation ●—● Normal for average age

TABLE IV.

Analysis of Cases of Chronic Heart Disease.

Lesion.	No. of Cases.	Rise.	% Rise.
Aortic Disease	15	12.6	17.0
Mitral Stenosis	3	10.7	10.7
Mitral Insufficiency	9	22.8	31.0
Non-valvular	15	17.2	21.4
Auricular Fibrillation	13	42.4	41.7

In Fig. XII the actual increase of rate under atropine is given in the series of cases of chronic heart disease and the curve of age increase at various ages in normal persons is inserted from Fig. IX for comparison.

Fig. XIII is a similar chart to the last except that % increase is charted instead of actual increase. The only difference between the two is that there are more cases above normal in XII than in XIII. This is due to the rapid initial rate in these cases reducing the % slightly.

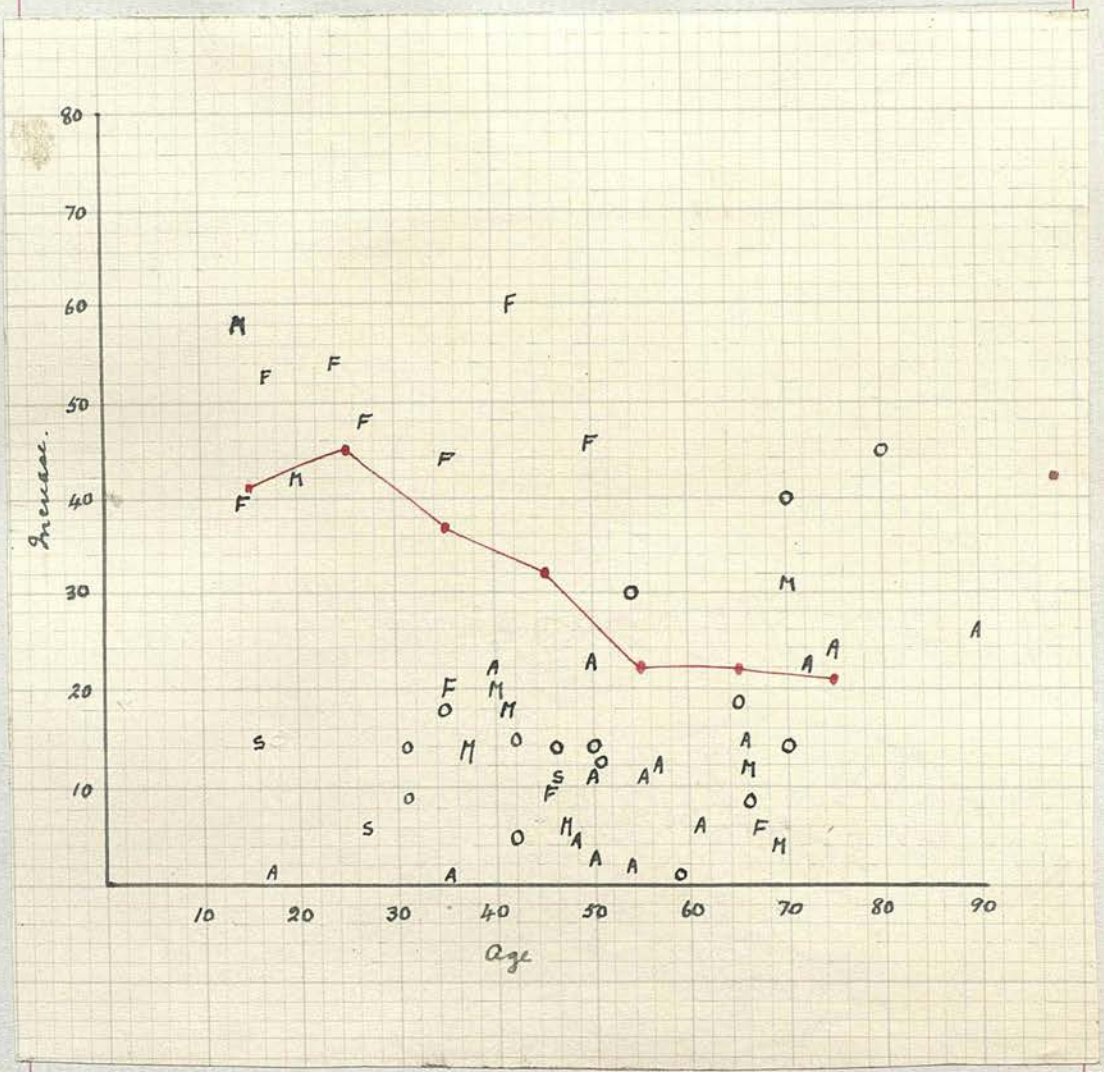

Fig. XII. Comparison of Actual increase after Atropine in Chronic Heart Disease with that of Normals at same age.

—— Normal Curve. A = Aortic.
S = Mitral Stenosis M = Mitral Insufficiency
O = Non Valvular F = Auricular Fibrillation

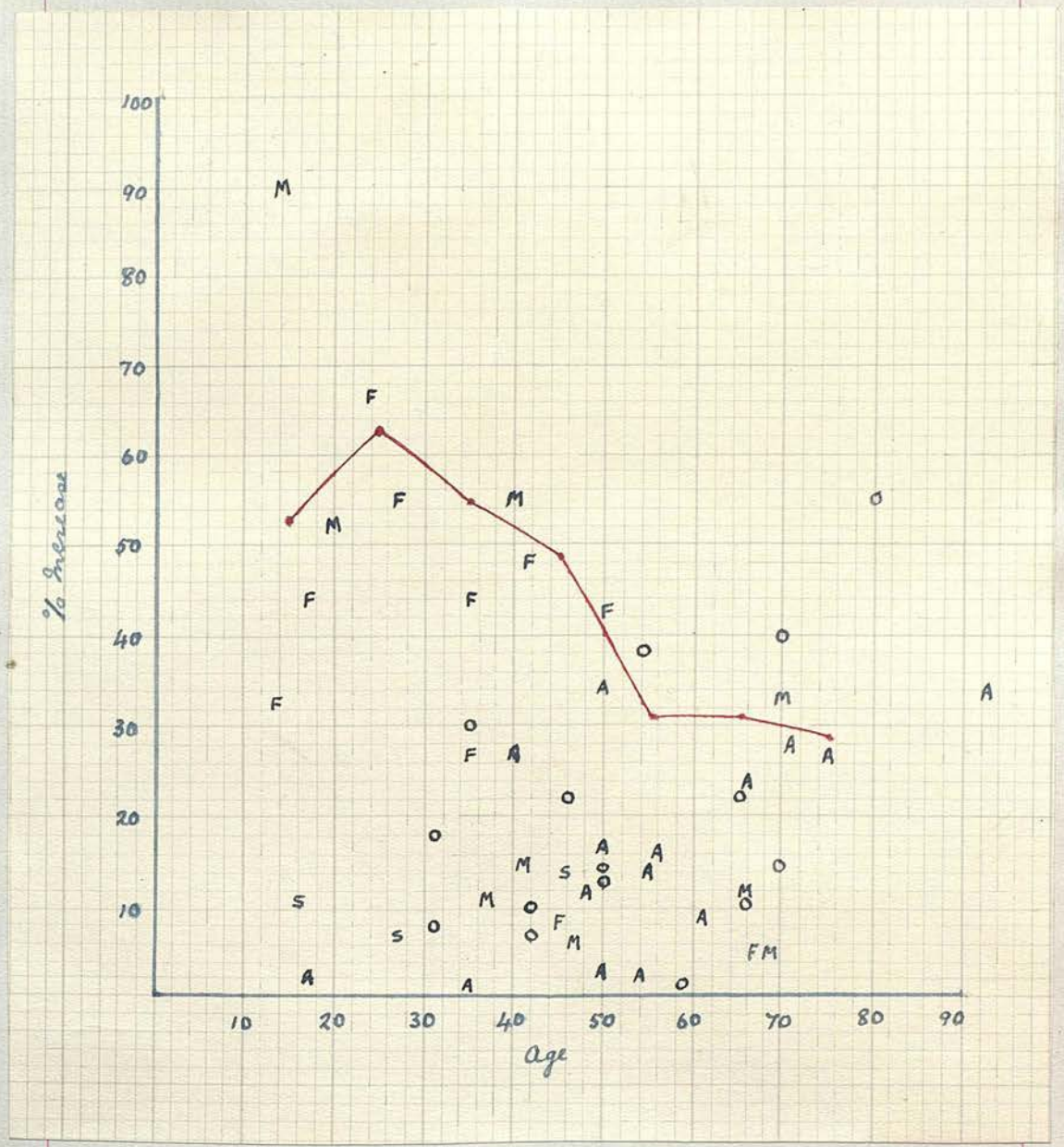

Fig. XIII. Comparison of % increase after Atropine in Chronic Heart Disease with that of Normals at same age.

—— Normal Curve
S = Mitral Stenosis
O = Non Valvular
A = Aortic.
M = Mitral Insufficiency.
F = Auricular Fibrillation.

Summary of Results.

It is seen that the increase in the vast majority of cases of heart disease is considerably below normal. The only exception to this is Auricular Fibrillation where the actual increase slightly exceeds normal for the corresponding age. These results support Muller's statement[64] that Aortic Disease shows a much greater reduction than other heart conditions. From the results obtained in the present series one might class Mitral Stenosis along with Aortic Disease. On examining Figs XII and XIII the difference although distinct is less marked than actually appears in Table IV. It is seen that the great majority of cases of Mitral Insufficiency and Non-Valvular Disease are well below normal although three cases of each show a very marked rise. As Table IV is composed of averages three cases with a large increase would considerably raise the average increase.

Fig. XI shows that in all the conditions examined except Aortic Disease the average initial rate was above normal. It is of course well known that the damaged heart tends to be more rapid than normal. It also shows that in Auricular Fibrillation the maximum rate attained after atropine administration is considerably greater than normal, while in Aortic Disease it is considerably below normal. The other conditions closely approximate to normal with Mitral Diseases slightly higher.

THE ACTION OF THE VAGUS IN AURICULAR FIBRILLATION UNDER THE INFLUENCE OF DIGITALIS.

In 1911 Mackenzie[54] quoted one case of this nature in which a considerable rise in heart rate was obtained after atropine administration. Cushny, Marris and Silberberg[16] next took up the subject and after a full investigation came to the conclusion that under digitalis the heart in auricular fibrillation was slowed from direct action on the muscle and not from stimulation of the inhibitory mechanism. Recently Lewis[52] reports a series of cases where a considerable rise in rate was obtained after atropine administration. He considers that the action is both on the cardiac muscle and on the inhibitory mechanism.

Table V gives details of my observations and Table VI shows the results of Cushny, Marris and Silberberg arranged in a similar manner.

TABLE V.

TABLE VI.

Fig. XIV shows the type of reaction obtained in Auricular Fibrillation under Digitalis after the administration of atropine. A curve has been inserted for comparison from Fig XI showing the type of reaction obtained in cases of Auricular Fibrillation not under the influence of Digitalis. Unfortunately these two curves have not been taken from the same cases. A curve for the normal age period in which the average age of these cases of Auricular Fibrillation fell has also been included.

TABLE V.

The Action of the Vagus in Auricular Fibrillation under Digitalis.

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose.	Rise.	% Rise.	Remarks.
1	26	X			73,130			1.9	57	78	
2	35		X		99,168			1.2	69	68	
3	39	X			88,120			1.3	32	36	
4	44		X			112,140		1.2	28	25	Exophthalmic Goitre.
5	45	X			77,73,148			1.3	71	91	
6	45		X			59,55,88		1.6	29	49	
6a					73,67,142			1.6	69	94	
7	51		X		76,65,110			1.4	34	46	
8	54		X		58,55,100			1.2	42	72	
9	59		X		92,175			1.2	83	90	
10	61	X			113,157			1.3	44	39	
11	65	X				72,92		1.6	20	28	

TABLE VI.

Auricular Fibrillation under Digitalis. (Cushny, Marris & Silberberg)

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose.	Rise.	% Rise.	Remarks.
1	12		X			70,96		1.2	26	37	
2	14		X				75,81	1.2	6	8	
3	17		X			77,92		1.2	15	19	
4	17	X					69,74	1.2	5	7	
5	24	X				69,86		1.2	17	25	
5a						57,84		1.2	27	48	
6	27	X				66,84		1.2	18	27	
7	35		X			62,84		1.2	22	35	
8	35	X			59,92			1.2	33	56	
9	45	X					52,59	1.2	7	13	
10	50	X			66,84			1.2	18	27	

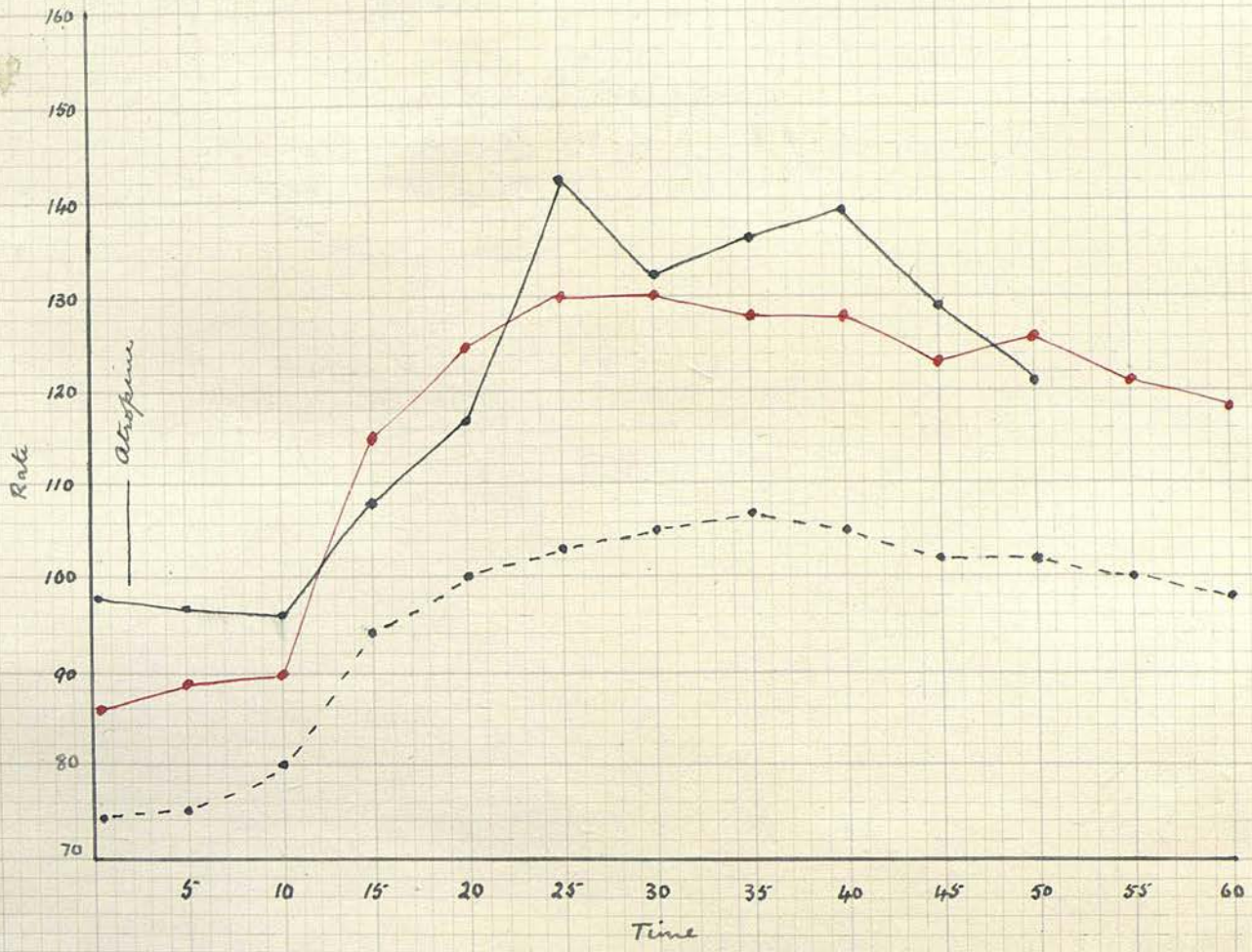

Fig. XIV. Effect of Vagal Release in Auricular Fibrillation under Digitalis compared to that in Auricular Fibrillation not under Digitalis and to normal for same age period.

●——● Auricular Fibrillation under Digitalis.

●——● Auricular Fibrillation not under Digitalis.

o----o Normal Curve.

TABLE VII.

Analysis of Cases of Auricular Fibrillation under Digitalis.

	No. of Cases.	Rise.	% Rise.
Present Series.	11	49.9	60.6
Cushny, Marris & Silberberg.	10	17.7	27.7

Fig. XV shows the % increase in rate under atropine in the present series of cases and also in the series of Cushny, Marris and Silberberg. The curve of percentage increase at various ages in normal persons is inserted from Fig. IX for comparison.

Fig. XV.

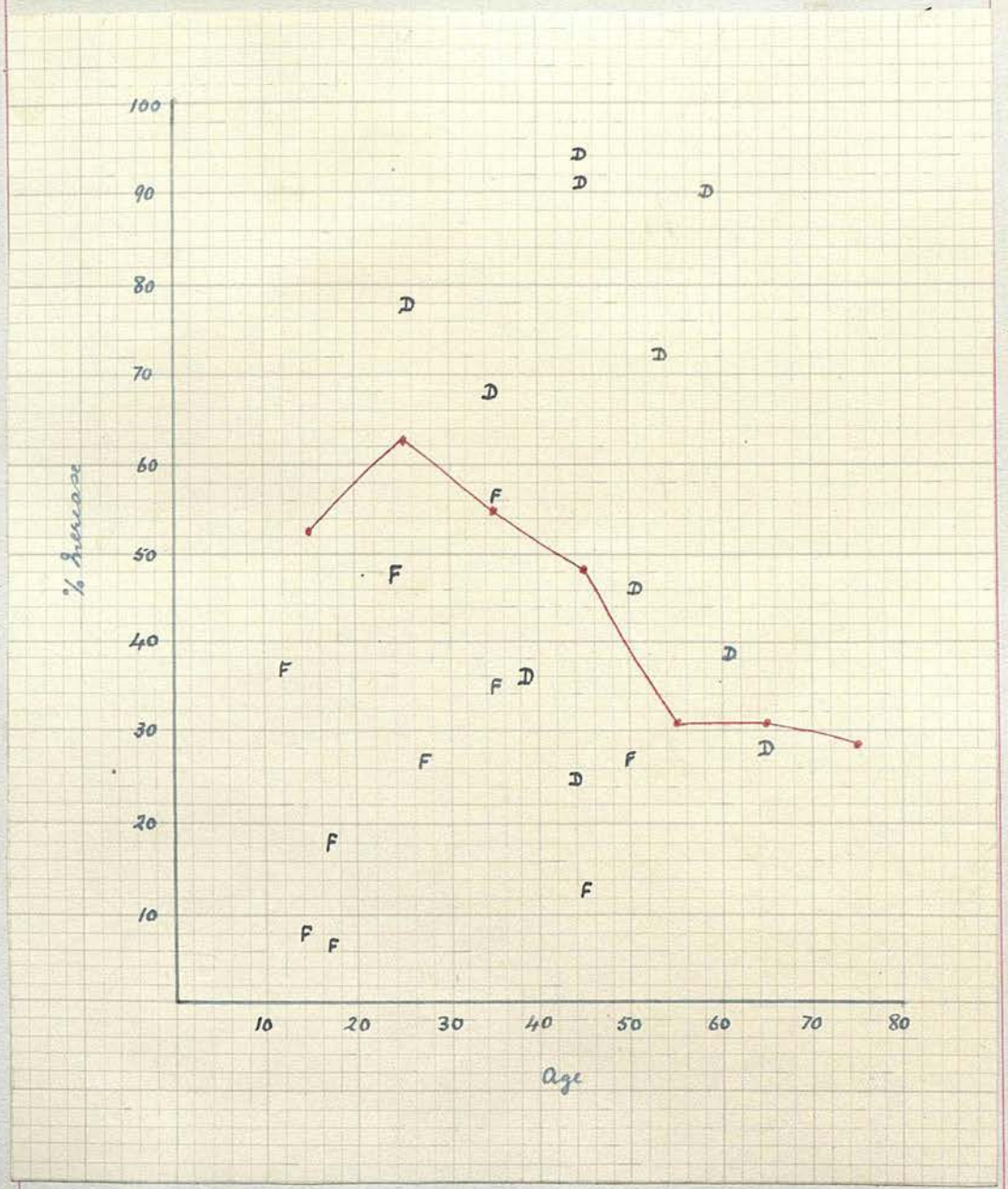

Fig. XV. Comparison of % increase in rate after atropine in Auricular Fibrillation under Digitalis with Normal persons of same age.

——— Normal Curve. D = Present series.

F = Cushny, Morris and Silberberg.

Summary of Results.

The results of the present series show that a considerable increase in rate can be obtained in Auricular Fibrillation when the heart is under the influence of Digitalis.

Unfortunately I did not have an opportunity of investigating the effect of atropine on these hearts without Digitalis but these results are considerably higher than comparable results obtained by Cushny, Marris and Silberberg and seem to show that the inhibitory mechanism is in part responsible for the slowing under Digitalis. The extent to which this is so cannot be correctly judged from Fig. XIV as the pre-digitalis curve was not taken from the same cases as the post-digitalis curve.

THE INFLUENCE OF THE VAGUS IN PRODUCING BRADYCARDIA.

The fact that some cases of Bradycardia are of vagal origin while others are not is well known. Table VIII is inserted to show the varied types of reaction which is obtained in this condition. The effect in this condition has been so frequently investigated that it seemed unnecessary to carry the work further in the present series.

TABLE VIII.

TABLE VIII.

The Influence of the Vagus in producing Bradycardia.

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose.	Rise.	% Rise.	Remarks.
1	18		X	Functional	54,120			1.6	66	122	
2	24	X		Cerebral Concussion			55,52,63	1.3	8	14	
3	45	X		Partial Heart Block.		48,75		2.3	27	56	

THE INFLUENCE OF THE VAGUS ON THE HEART RATE IN CASES OF GOITRE.

No previous work has been done on the vagus control of the heart in this condition. As the heart rate is so profoundly altered in cases of Exophthalmic Goitre it was thought that this problem would provide a profitable line of investigation.

Table IX gives details of the cases of Exophthalmic and Parenchymatous Goitre investigated.

TABLE IX.

Fig. XVI shows the type of reaction obtained in each variety of Goitre after atropine administration. A curve of the type of reaction obtained in normal persons in the age group corresponding to the average age of the goitre cases has been inserted for comparison.

Fig XVI./

THE INFLUENCE OF THE VAGUS ON THE HEART RATE IN CASES OF GOITRE.

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Fig XVI./

TABLE IX.

The influence of the Vagus on the Heart Rate in Goitre.

Exophthalmic Goitre.

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose	Rise	% Rise	Remarks.
1	18		X	Exophthalmic Goitre.	127,180			1.5	53	42	
2	21		X	"	107,158			1.5	51	47	
3	21		X	"	107,100,140			1.4	33	30	
4	21		X	"		103,120		1.8	17	16	
5	23		X	"		139,132,168		1.5	29	21	
6	29		X	"	86,72,144			2.0	58	67	
7	33		X	"		81,108		1.6	27	33	
8	38		X	"	90,120			1.5	30	33	
9	41		X	"		110,108,126		1.5	16	14	
10	51		X	"			159,160	2.0	1	-	13/5/21.
10a						106,120		1.5	14	13	8/7/21.

Parenchymatous Goitre.

1	11		X	Parenchymatous Goitre.	98,79,150			0.8	52	53	
2	15		X	"	80,66,144			1.4	64	80	
3	17		X	"	80,66,132			1.5	52	65	
4	19		X	"	80,75,110			1.4	30	37	

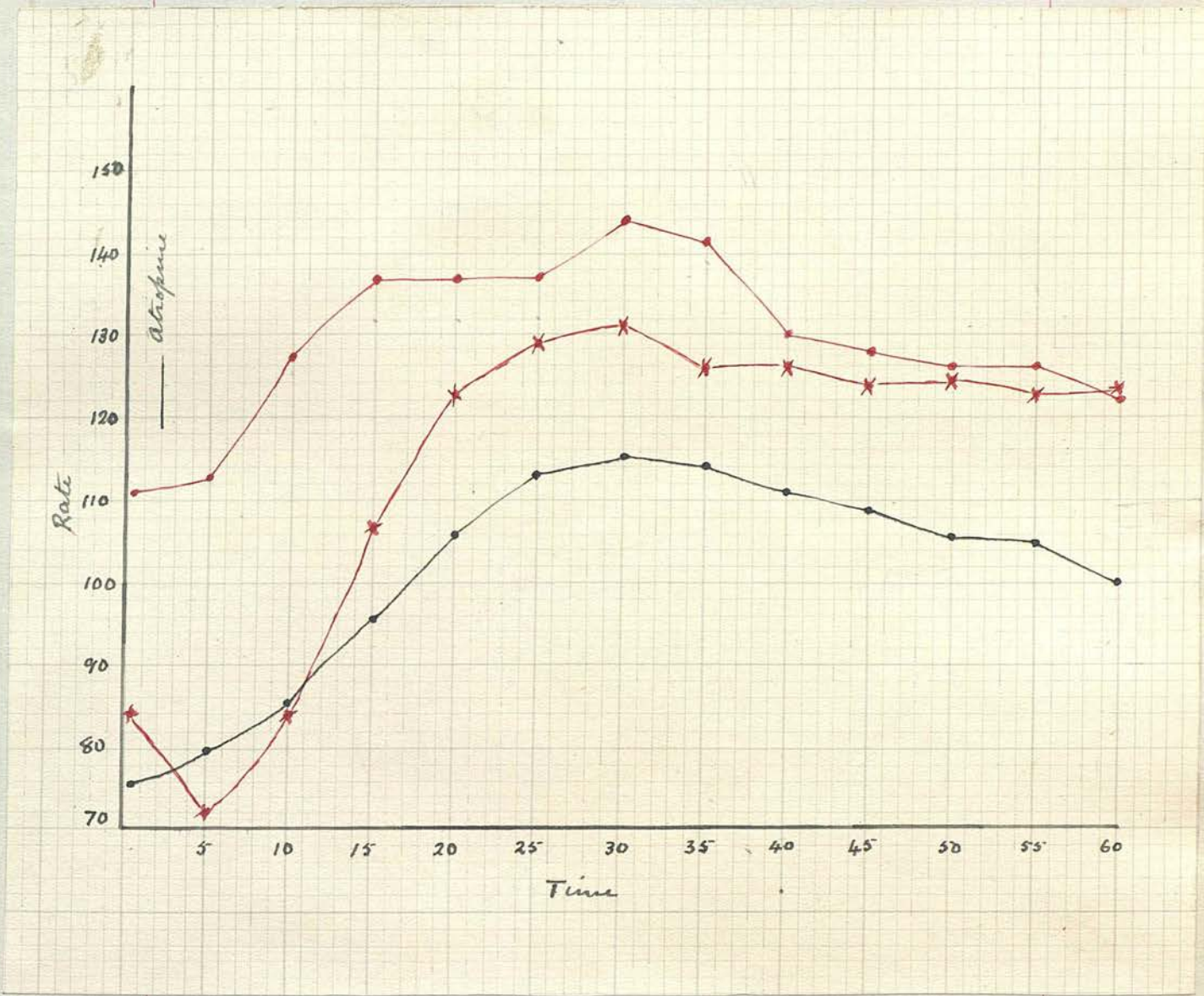

Fig. XVI. Effect of Vagal Release in cases of Goitre compared to normal for same age period.

●——● Exophthalmic Goitre.
x——x Parenchymatous Goitre.
●——● Normal Curve.

TABLE X.

Analysis of Goitre Cases.

Disease.	No of Cases.	Rise.	% Rise.
Exophthalmic Goitre.	10	31.5	30.3
Parenchymatous Goitre.	4	49.5	57.0

In Fig. XVII the actual increase in rate under atropine in the present series of cases of Goitre is given and the curve of increase at various ages in normal persons is inserted from Fig. IX for comparison.

Fig. XVIII is a similar chart to the last except that % increase is used instead of actual increase.

Fig. XVII./

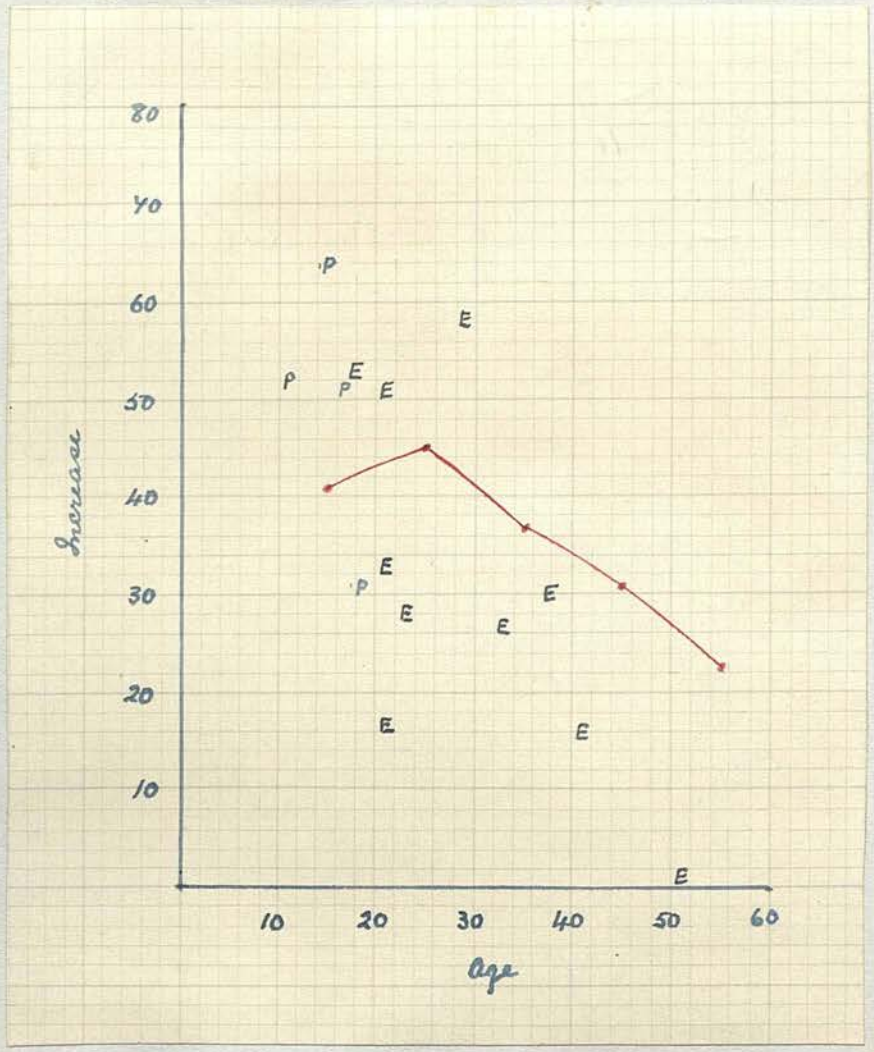

Fig. XVII. Comparison of actual increase in rate after Atropine in Goitre with normal persons of the same age.

——— Normal Curve.

E = Exophthalmic Goitre.

P = Parenchymatous Goitre.

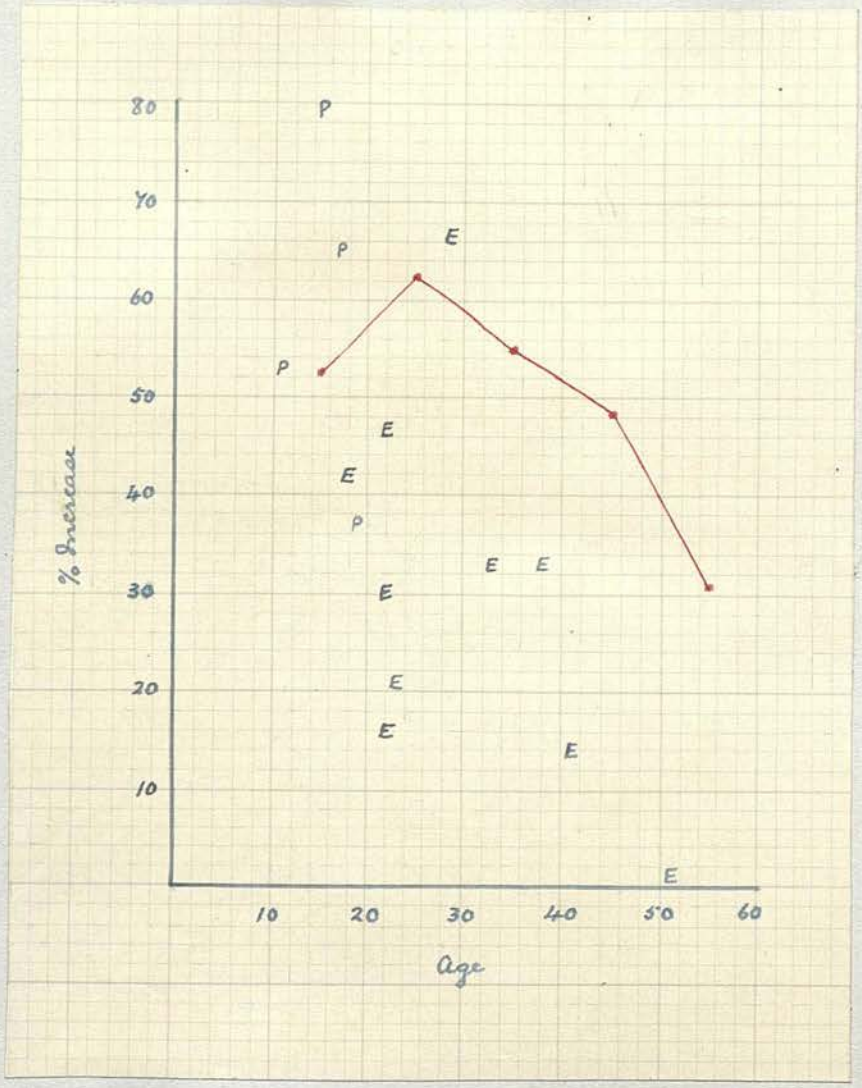

Fig. XVIII. Comparison of % increase in rate after Atropine in Goitre with normal persons of same age.

—— Normal Curve.

E = Exophthalmic Goitre.

P = Parenchymatous Goitre.

Summary of Results.

These results show that there is in the majority of cases of Exophthalmic Goitre an increase below normal while cases of Parenchymatous Goitre, as is to be expected, fall within normal limits.
Fig. XVI shows that the original rate is considerably increased in Exophthalmic Goitre and that the maximum height attained is considerably above normal.
Cases of Parenchymatous Goitre also reach a greater height than normal. The original rate in the former however is slightly higher and if the two curves were started from the same point they would be seen to correspond very closely.

THE INFLUENCE OF THE VAGUS ON THE HEART RATE IN FEBRILE CONDITIONS DURING CONVALESCENCE.

The first work on this subject was the admirable work of Marris in Typhoid Fever[57]. I have worked out his results in this condition along the lines of this report and give his results both in cases during the febrile and afebrile stages. Rheumatic Fever and Pneumonia are known to have a permanent or temporary bad effect on this heart, therefore they were selected for study in the present observations. Cases during convalescence were selected as it had been shown by Marris that temperature affected the reaction although despite this in no type of fever did he get such consistent low results as in Typhoid Fever. If febrile cases were used and varying results obtained it would be difficult to be certain that the varying effect was not due to the temperature rather than to the disease per se. It was also difficult to get cases with temperature weighed and thus regulate the dosage according to the technique of these observations. Chorea has been included in this group as it is so closely related in its effect on the heart to Rheumatic Fever.

Table XI gives the details of the cases of Pneumonia, Rheumatic Fever and Chorea investigated, and Table XII gives the results of Marris in cases of Typhoid Fever. The latter are only given in age groups as details will be found in Marris' Report.

TABLE XI.

The influence of the Vagus on the Heart Rate in Fevers during Convalescence.

Pneumonia.

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small	Dose.	Rise.	% Rise.	Remarks.
1	18	X		Lobar		79,72,97		1.5	18	23	
2	21	X		"		90,84,114		1.2	24	26	
3	24	X		Broncho		75,91		1.8	16	21	
4	25		X	Lobar		62,60,90		1.5	28	45	
5	28	X		"		84,74,102		1.4	18	21	
6	30		X	"	69,66,132			1.5	63	91	
7	32	X		Broncho		80,72,108		1.7	28	35	
8	33	X		Lobar	72,60,102			1.8	30	41	
9	36	X		"		69,96		1.3	27	39	
10	48	X		Broncho.		90,102		1.3	12	13	
						Rheumatic Fever.					
1.	13	X			66,60,120			0.9	54	82	
2	14		X		62,57,125			1.3	63	101	
3	15	X			91,90,144			1.2	53	58	
4	15	X			85,156			1.2	71	83	
5	19	X			62,57,94			1.8	32	51	
6	21		X		92,138			1.5	46	50	
7	21	X			84,132			1.3	48	57	
8	24	X			81,75,150			2.0	69	85	
9	26		X		108,93,165			1.4	57	53	
10	29		X		62,57,94			1.8	32	51	

Chorea./

TABLE XI. (Contd.)

Chorea.

No.	Age.	M.	F.	Disease.	Large.	Medium.	Small.	Dose.	Rise.	% Rise.	Remarks.
1	11		X		68,150			0.6	82	120	
2	12		X		81,78,132			1.3	51	63	
3	15		X		89,132			1.4	43	48	
4	16		X		69,126			1.5	57	82	
5	17		X		93,156			1.3	63	68	

TABLE XII.

Typhoid Fever. (Marris[57])

Febrile.

Age.	Number of Observations.	Rise.	% Rise.
10 - 20	22	10.2	13.7
20 - 30	98	8.5	10.2
30 - 40	9	12.9	18.2
Age not stated.	31	8.0	11.4
		Afebrile.	
10 - 20	3	14.3	19.3
20 - 30	32	18.2	25.6
30 - 40	12	15.4	20.8
Age not stated.	7	8.8	9.6

Dose of Atropine Sulphate in all cases $\frac{1}{33}$gr.

Fig. XIX shows the type of reaction obtained in these conditions and the curve of the normal age group corresponding to the average age of the cases investigated has been inserted for comparison.

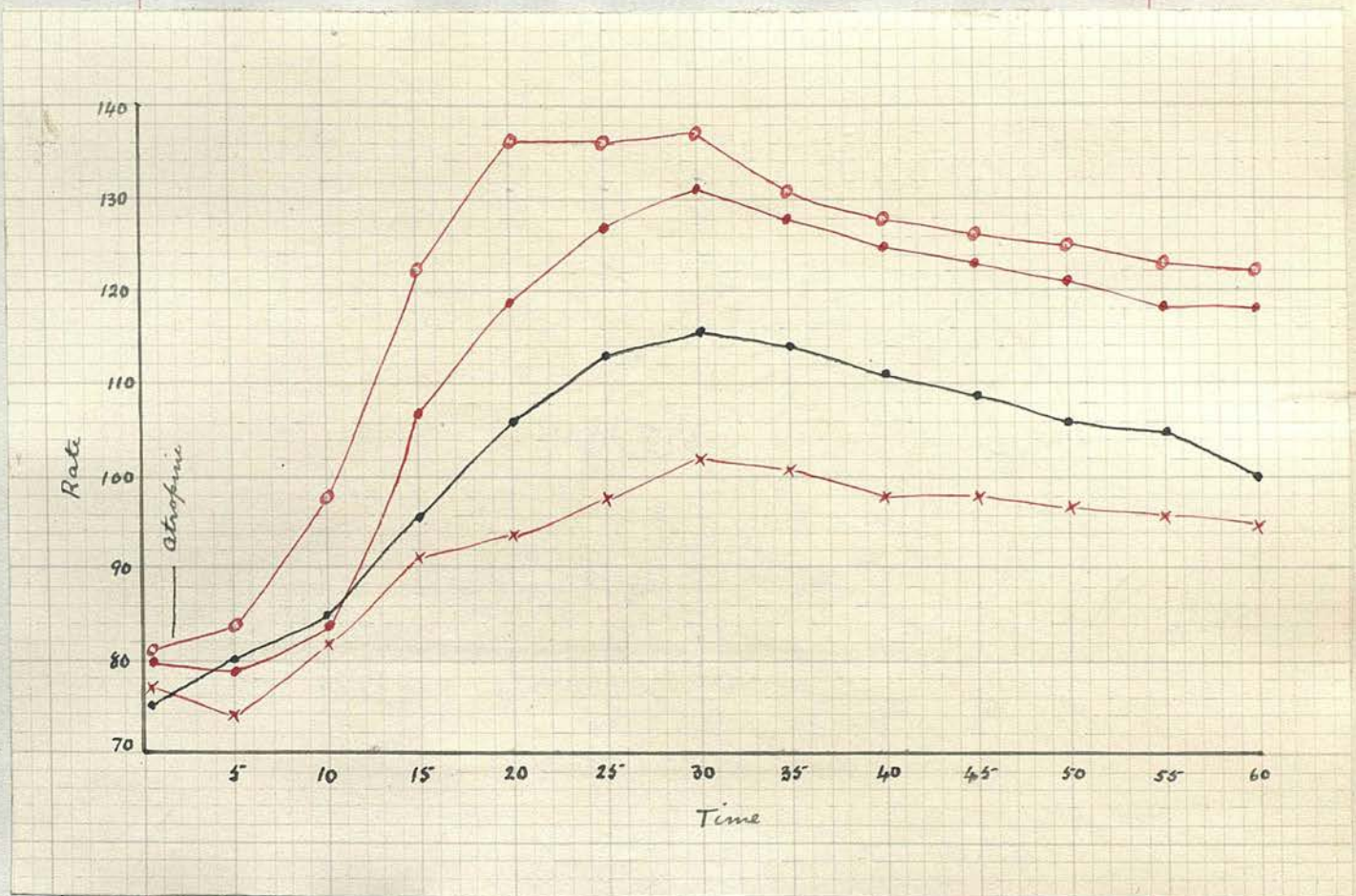

Fig. XIX. Effect of Vagal Release during Convalescence from Rheumatic Fever, Chorea and Pneumonia compared to normal for same age period.

●——● Rheumatic Fever.
○——○ Chorea.
×——× Pneumonia.
●——● Normal Curve.

TABLE XIII.

Analysis of Cases of Fever during Convalescence.

Disease.	No. of Cases.	Rise.	% Rise.
Pneumonia.	10	26.4	35.5
Rheumatic Fever.	10	52.5	67.1
Chorea.	5	59.2	76.2
Typhoid (Marris)			
All Cases	214	7.7	10.1
Febrile	160	6.9	11.3
Afebrile	54	16.2	22.1

In Fig. XX the actual increase in rate under atropine in the present series of post febrile cases is given and the curve of increase at various ages in normal persons is inserted from Fig. IX for comparison.

Fig. XXI is a similar chart to the last except that percentage increase is compared instead of actual increase.

Fig. XX./

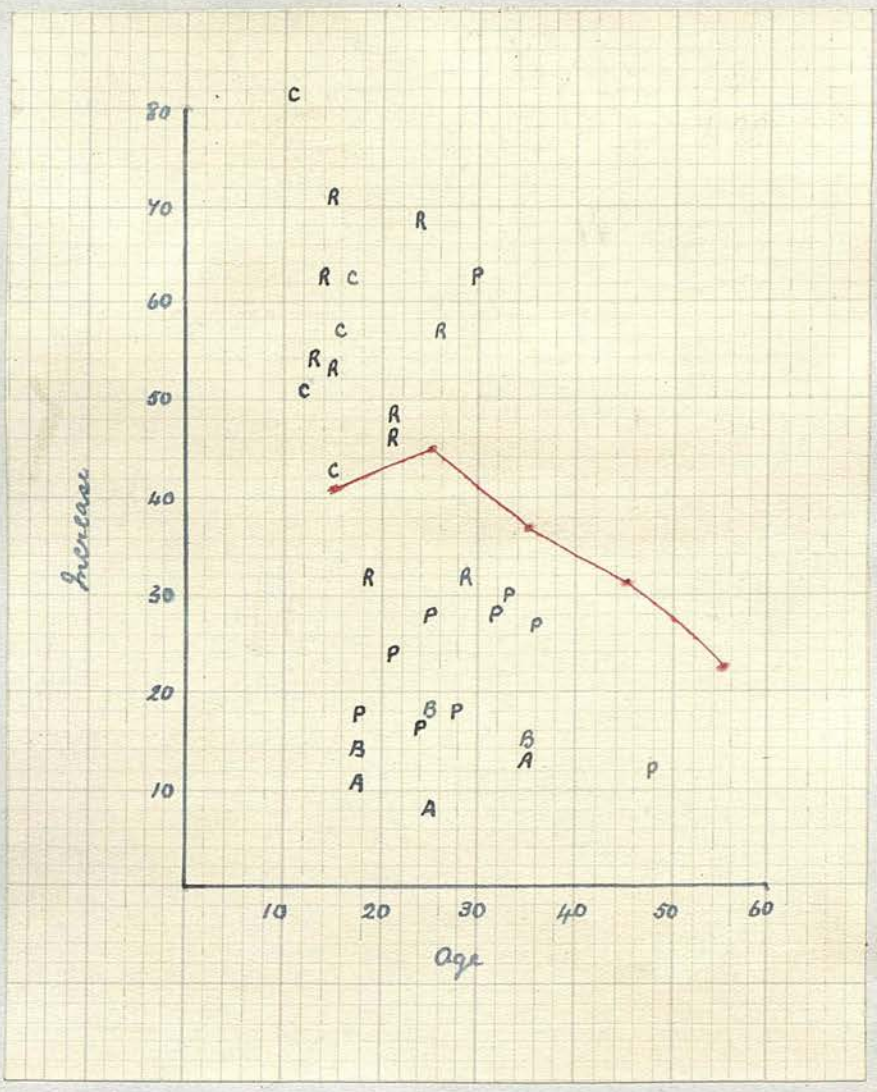

Fig. XX. Comparison of Actual Increase in rate after Atropine during convalescence from Rheumatic Fever, Chorea, Pneumonia and during the febrile and afebrile stages of Typhoid Fever with that of normal persons of same age.

——— Normal Curve.
R = Rheumatic Fever.
C = Chorea.
P = Pneumonia.
A = Typhoid (febrile).
B = Typhoid (afebrile).

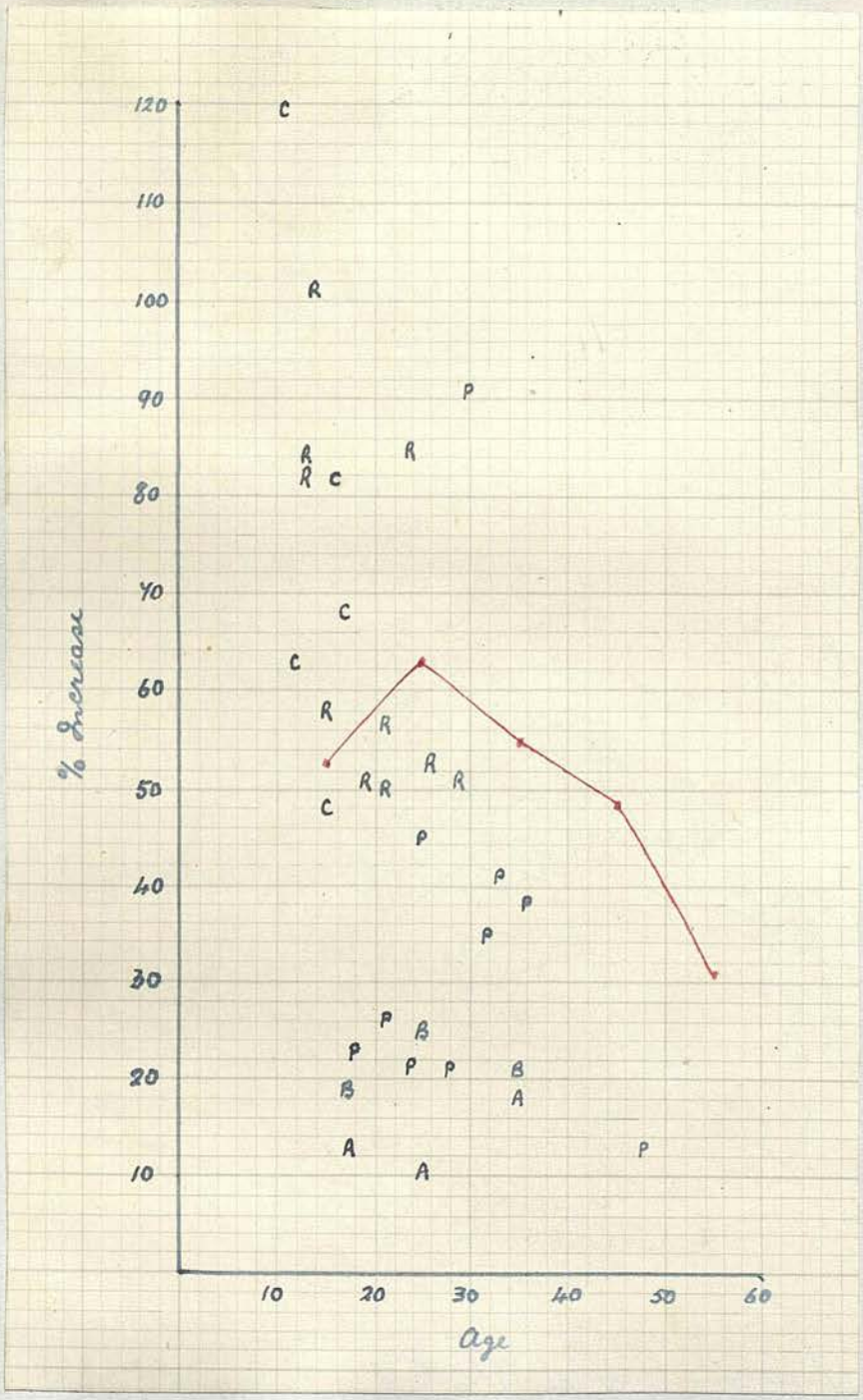

Fig. XXI. Comparison of % Increase in Rate after Atropine during convalescence from Rheumatic Fever, Chorea, Pneumonia and during the febrile and afebrile stages of Typhoid Fever with that of normal persons of same age.

——— Normal Curve.
R = Rheumatic Fever.
C = Chorea.
P = Pneumonia.
A = Typhoid (febrile).
B = Typhoid (afebrile).

Summary of Results.

These results show that after Rheumatic Fever and Chorea the increase in rate after atropine administration is considerably greater than normal while in Typhoid Fever and after Pneumonia it is considerably less. It is seen that the reduction is greater in febrile cases of Typhoid than in afebrile. Table XI shows that there is no appreciable difference between Lobar and Broncho-pneumonia. No relation in Pneumonia could be found between the time which had elapsed from either the onset of disease or the crisis to the performance of the test and the ultimate increase in rate obtained.

THE INFLUENCE OF THE HEART RATE ON THE TONICITY OF THE CARDIO-INHIBITORY CENTRE.

It has been shown in the physiological review of the functions of the vagus that the tonicity of the centre can be profoundly altered by afferent stimuli. A considerable amount of evidence has been brought forward notably by Bambridge[6] and Eyster and Hooker[23] that the heart and great vessels play a considerable part in the regulation of the tonicity of the cardio-inhibitory centre. A problem which might have considerable bearing on the present investigation seemed to be.- If the heart is beating more rapidly than normal is the tonicity of the centre increased and if it is beating more slowly than normal is the tonicity reduced? If this is found to be so is it due respectively to a greater and lesser number of afferent impulses passing from the heart and great vessels and affecting the centre.

The method selected for estimating the tonicity of the centre was to cut one vagus and to find a stimulus which applied to the central end produced a definite slowing of the heart. The alteration of rate was then produced and the same stimulus was again applied/

applied for approximately the same length of time. To complete the experiment the rate was allowed to return to normal and the same stimulus reapplied.

The difficulties in technique were considerable. The cardio-inhibitory centre is so sensitive that unless great care is taken in the experiments the power of the centre to be affected by stimulation of the central end of one vagus is completely lost.

In the earlier experiments cats were used but later dogs were used entirely.

The following are the principal technical difficulties which had to be overcome.

Anaesthetic. This provided one of the greatest obstacles. The deleterious effect of many anaesthetics on the centre is well known. The first anaesthetic used was Paraldehyde but no successful results were obtained as the centre was found to be inactive. Decerebrated cats were next tried but the shock of decerebration was so much that the centre was found in most cases to be inactive. Ether given continuously was tried but with no better results. Then an endeavour was made to dispense with anaesthesia as far as possible by trephining the dog's skull and destroying the brain so that the further manipulations could be carried out/

out without anaesthesia. Only one case however was successful as the operative procedures were so severe. The next anaesthetic used was Morphine and Chloretone. When the Chloretone was given in aqueous solution by the stomach it was found very difficult to anaesthetize the dog in a reasonable time. It was therefore decided to give Chloretone in alcohol by the stomach. The dosage in this was however very difficult to adjust so finally the intramuscular injection of Chloretone in alcohol was used. This proved to be by far the most satisfactory method and in practically all cases a satisfactory reflex slowing could be produced under this method of anaesthesia.

The procedure is as follows. Two hours before the commencement of the experiment a subcutaneous injection of Morphine (20 mg. per kilo) is given. Half an hour later an intramuscular injection of Chloretone (0.2 gm. per kilo dissolved in 5 cc. of 90% alcohol) is given. If the dog is not satisfactorily anaesthetised an hour and a half later a further 0.1 gm. per kilo of Chloretone is given and in every case this was found to produce a satisfactory anaesthesia.

Blood-pressure./

Blood-pressure. In order to obtain a satisfactory result the blood pressure must be at not less than 60 mm. Hg. at the commencement of the stimulation and an endeavour must be made to carry out the experiment before it falls to any considerable extent.

Operation. The operative procedures must be carried out as quickly as possible, unnecessary shock must be avoided and bleeding must be reduced to a minimum as all these factors lower the activity of the centre.

During the experiment all afferent stimuli from other parts than the heart must be reduced to a minimum. In most cases the thorax was opened and in these the rate of artificial respiration was kept constant throughout the experiment.

Method of producing alterations in Rate.

Three different methods have been used.-

(1) The intravenous injection of Quinine Hydrochloride or Bile to slow the heart by direct action on the muscle. This method was only used in a few experiments for reasons to be stated later.

(2) The application of heat or cold to the sino-auricular node.

(3) Stimulation of the Accelerator nerves to produce quickening and stimulation of the peripheral end of the cut vagus to produce slowing.

Protocols of Experiments.

Expt. I. 19.10.21. Cat, 2300 gm. Ether. Decerebrated. Trachea cannula. Left Vagus cut. Right carotid attached to Hurtle's manometer. Artificial respiration. Thorax opened. B.P. 62 mm. Hg. Slowing produced by applying cold to sino-auricular node. Stimulus used 10 cm. Drum tracing. Time in 1".

Expt. II. 20.10.21. Cat, 2500 gm. Ether. Decerebrated. Operation and recording same as Expt. I. B.P. 60 mm. Hg. Alterations in rate produced by applying heat and cold to sino-auricular node. Stimulus - heat 20 cm. - cold 10 cm. Drum tracing. Time in 1".

Expt. III. 7.11.21. Dog, 10 kilos. Ether. Tripened and cerebrum destroyed. Trachea cannula. Left vagus cut. Right carotid attached to Hg. and Hurtle's manometer. Artificial respiration. Thorax opened. Right stellate ganglion dissected out and quickening produced by stimulating the accelerator nerves. B.P. 55 mm. Hg. Stimulus used 8 cm. Drum tracing. Time in 1".

Expt. IV. 2.12.21. Dog, 15 kilos. Morphine and intramuscular chloretone. Trachea cannula. Right/

Right carotid attached to Hg. manometer and Left attached Hurtle's manometer. Left Vagus cut. Cannula in jugular vein. B.P. 70 mm. Hg. Stimulus 8 cm. 38 cc. of Bile in water given intravenously to slow the heart. The Bile had been purified by precipitation with alcohol. The alcohol was afterwards evaporated off and water added to make a solution. Drum tracing. Time in 1".

Expt. V. 7.12.21. Dog, 12 kilos. Morphine and intramuscular Chloretone. Trachea cannula. Right carotid attached to Hurtle's and Hg. manometers. Left Vagus cut. Cannula in jugular vein. B.P. 65 mm. Hg. Stimulus 8 cm. 17 cc. Quinine Hydrochloride in Saline (1 cc. = 20 mg.) given intravenously to slow the heart. Drum tracing. Time in 1".

Expt. VI. 1.2.22. Dog, 16 kilos. Morphine and intramuscular Chloretone. Trachea cannula. Right carotid attached to Hg. and Hurtle's manometers. Left Vagus cut. Artificial respiration. Thorax opened. B.P. 62 mm. Hg. Stimulus 8 cm. Alterations in rate caused by applying cold and later heat to the sino-auricular node. Drum tracing. Time in 1".

Expt. VII./

Expt. VII. 9.2.22. Dog, 7½ kilos. Morphine and intramuscular Chloretone. B.P. 60 mm. Hg. Same experiment as Expt. VI.

Expt. VIII. 13.6.22. Dog, 18 kilos. Morphine and intramuscular Chloretone. Trachea cannula. Right carotid attached to Hg. manometer. Left Vagus cut. B.P. 68 mm. Hg. Stimulus 10 cm. Slowing produced by weak Faradic stimulation of the peripheral vagus. Drum tracing. Time in 1".

Expt. IX. 16.6.22. Dog, 7 kilos. Morphine and intramuscular Chloretone. Trachea cannula. Right carotid attached to Hg. manometer. Left Vagus cut. Artificial respiration. Thorax opened. Right stellate ganglion dissected out. B.P. 64 mm. Hg. Stimulus 14 cm. Slowing produced by weak Faradic stimulation of the peripheral vagus. It was intended to stimulate the accelerators and produce quickening but the ligature slipped and they could not be found. Drum tracing. Time in 1".

Expt. X. 20.6.22. Dog, 8 kilos. Morphine and intramuscular Chloretone. B.P. 65 mm. Hg. Stimulus /

Stimulus 8 cm. Same operative procedures as in Expt. IX. Heart quickened by accelerator stimulation and later slowed by weak Faradic stimulation of the peripheral vagus. Drum tracing. Time in 1".

Expt. XI. 30.6.22. Dog, 9 kilos. Morphine and intramuscular Chloretone. B.P. 60 mm. Hg. Same experiment as Expt. X except that right vagus cut instead of left. Stimulus 8 cm. Drum tracing. Time in 1".

Expt. XII. 3.7.22. Dog, 5 kilos. Morphine and intramuscular Chloretone. Same experiment as Expt. VI except that only Hg. manometer used to record results. B.P. 70 mm. Hg.

Table XIV gives the results obtained in these experiments. In each case the stimulus is kept constant throughout the three observations. In each case the normal observations were taken immediately before the alteration in rate and as soon as the heart had returned to normal. Although slowing and quickening observations were made in some cases on the same animal the normal may have altered during the time the methods were being altered, therefore a fresh series of normal observations is necessary.

TABLE XIV.

Alterations in rate produced by central vagal stimulation while heart is beating at normal and abnormal rates.

A. Slow Rate.

Expt.	Central Vagal Stim.	Before slowing. Orig. Rate.	Rate on Stim.	Fall.	% Fall	During slowing. Orig. Rate.	Rate on Stim.	Fall.	% Fall.	After Recovery. Orig. Rate.	Rate on Stim.	Fall.	% Fall.
I.	10 cm.	228	120	108	47	156	108	48	31	222	106	116	52
II.	10	210	70	140	67	150	78	72	48	210	82	128	61
IV.	8	144	92	52	36	124	110	14	11	Drug administered. No return to original rate.			
V.	8	170	120	50	29	140	94	46	33	"	"	"	"
VI.	8	139	110	29	21	127	105	22	17	135	110	25	19
VII.	8	174	145	29	17	138	108	30	22	182	150	32	18
VIII.	10	135	105	30	22	120	100	20	17	130	130	0	0
IX.	14	85	73	12	14	75	65	10	13	103	90	13	13
X.	8	135	105	30	22	118	93	25	21	130	88	42	30
XI.	8	135	115	20	15	80	67	13	16	142	105	37	26
XII.	8	165	124	41	25	130	100	30	23	155	136	19	12

B. Rapid Rate.

II.	20	200	112	88	44	230	100	130	56	190	112	78	41
III.	8	150	105	45	30	210	90	120	57	140	90	50	36
VI	8	135	110	25	18	185	155	30	17	150	122	28	19
VII.	8	182	150	32	18	215	190	25	12	184	168	16	9
X.	8	132	112	20	15	195	140	55	28	130	88	42	32
XI.	8	120	92	28	23	160	140	20	12	142	105	37	26
XII.	8	165	124	41	25	210	150	60	29	155	136	19	12

Figs. XXII - XXVI are photographs of tracings obtained in these investigations. They show the type of result obtained by each of the methods used. The normal tracings are shown as well as those obtained during the alteration of rate. In each of these A = Before alteration in rate, B = During alteration in rate, C = After recovery. Time in all = 1".

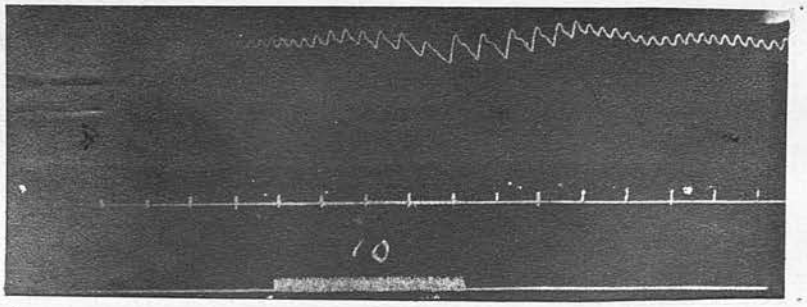

Fig. XXII A.

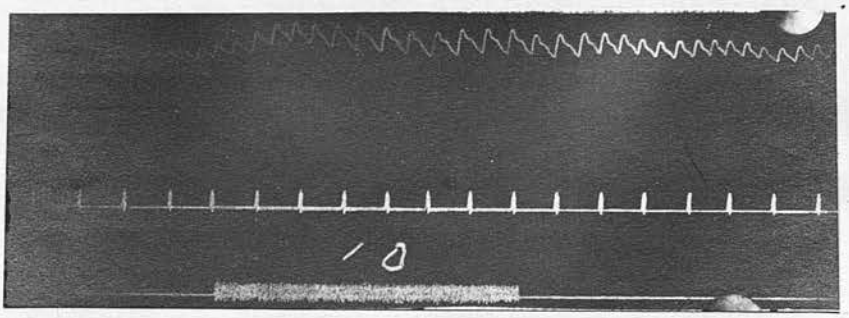

Fig. XXII B.

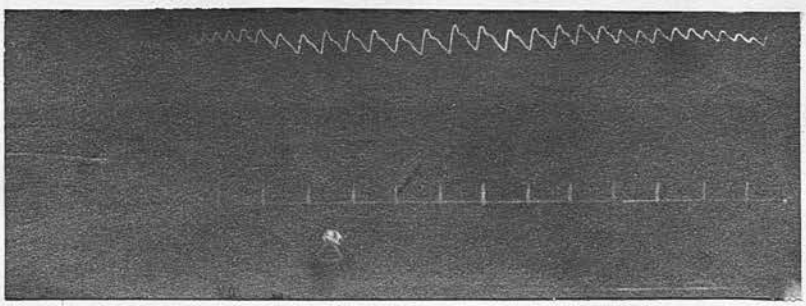

Fig. XXII C.

Fig. XXII. Effect of central vagal stimulation when heart slowed by cold applied to sino-auricular node. Vagal stimulus 10 cm.

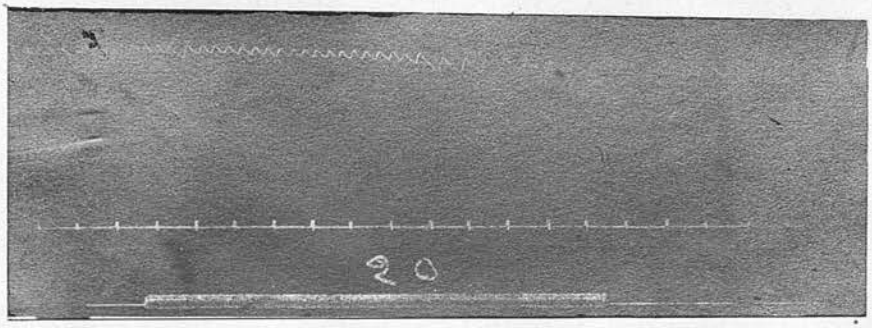

Fig. XXIII A.

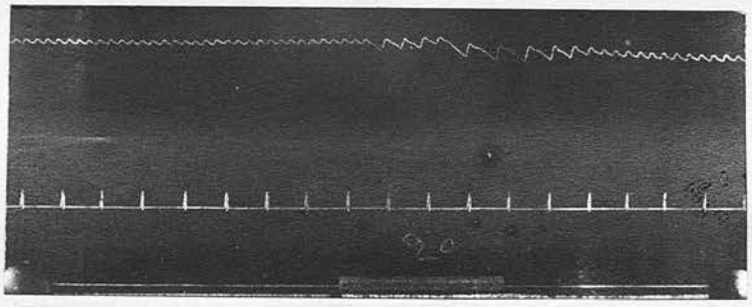

Fig. XXIII B.

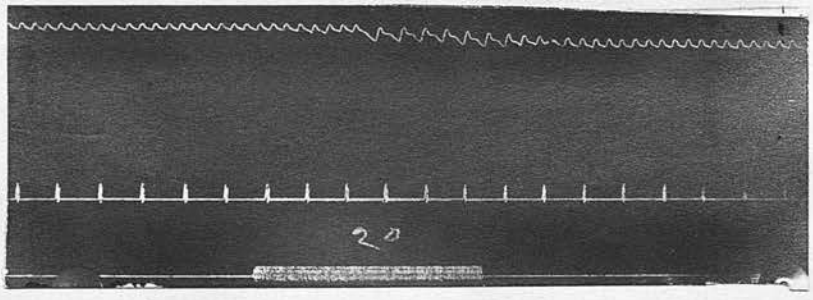

Fig. XXIII C.

Fig. XXIII. Effect of central vagal stimulation when heart quickened by heat applied to Sino-auricular node. Vagal stimulus 20 cm.

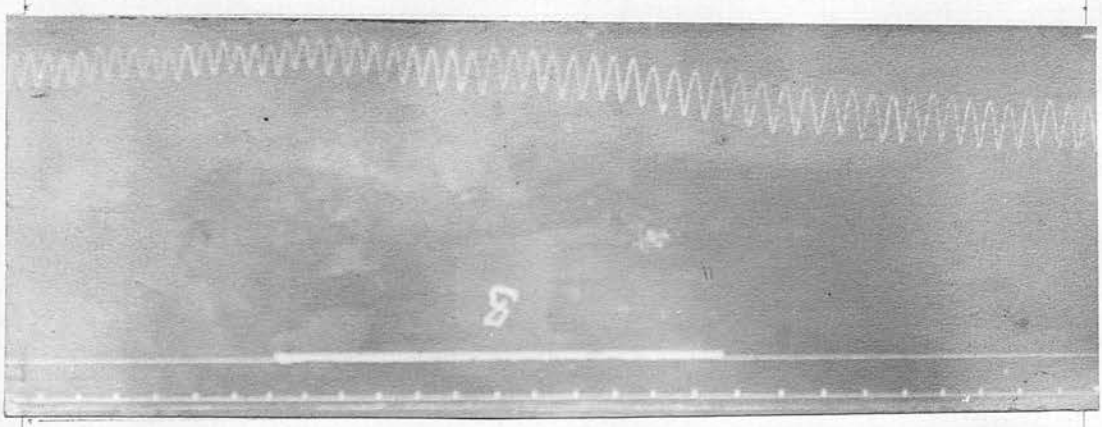

Fig. XXIV A.

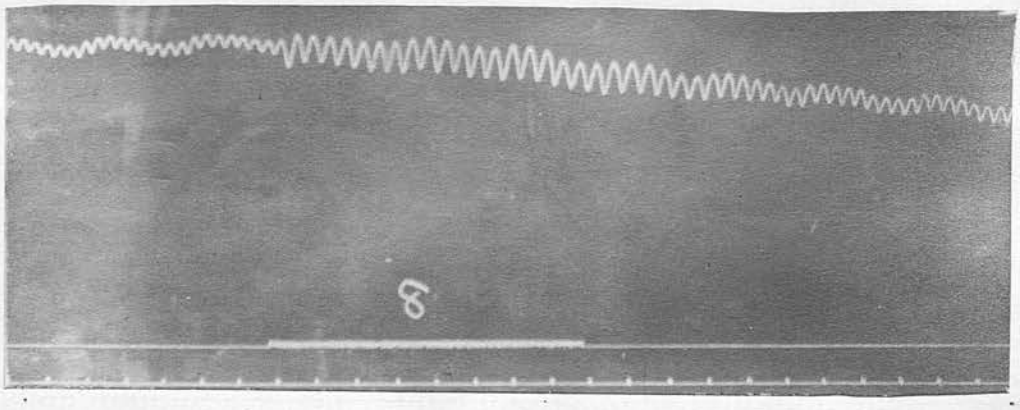

Fig. XXIV B.

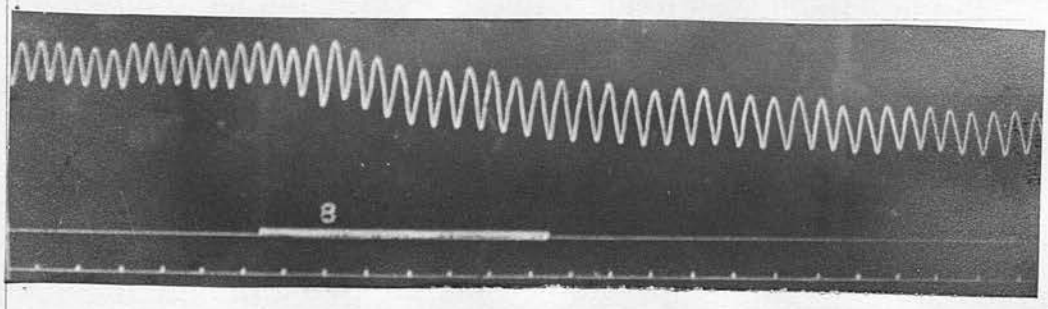

Fig. XXIV C.

Fig. XXIV. Effect of central vagal stimulation when heart quickened by accelerator stimulation. Vagal Stimulus 8 cm.

Note in C the height of the recorder of B.P. altered to get the tracing on one paper. Actual B.P. in C. = 60 mm. Hg.

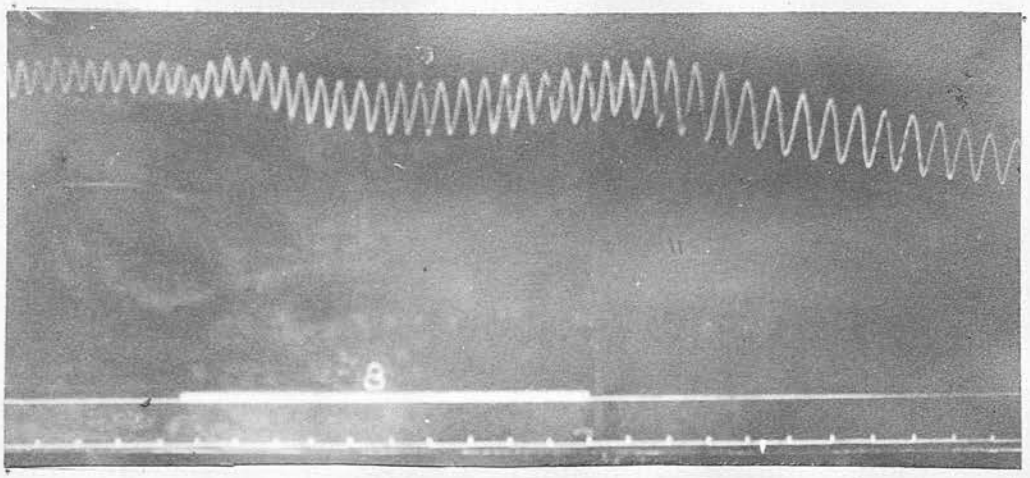

Fig. XXV A.

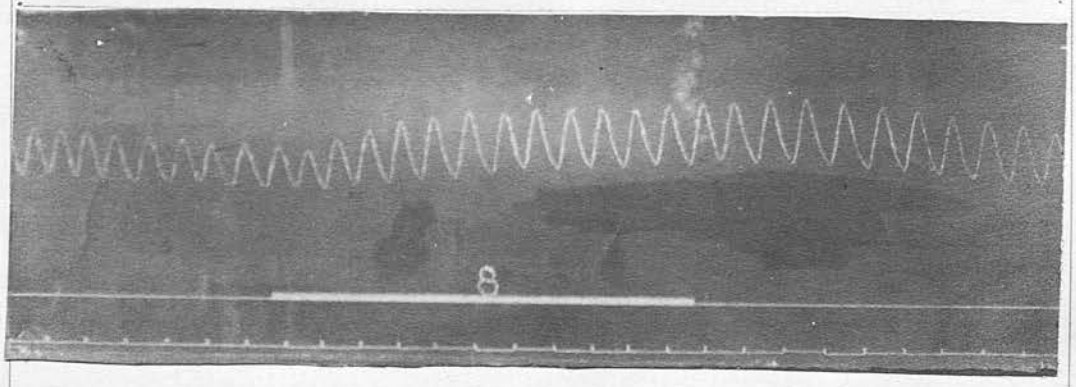

Fig. XXV B.

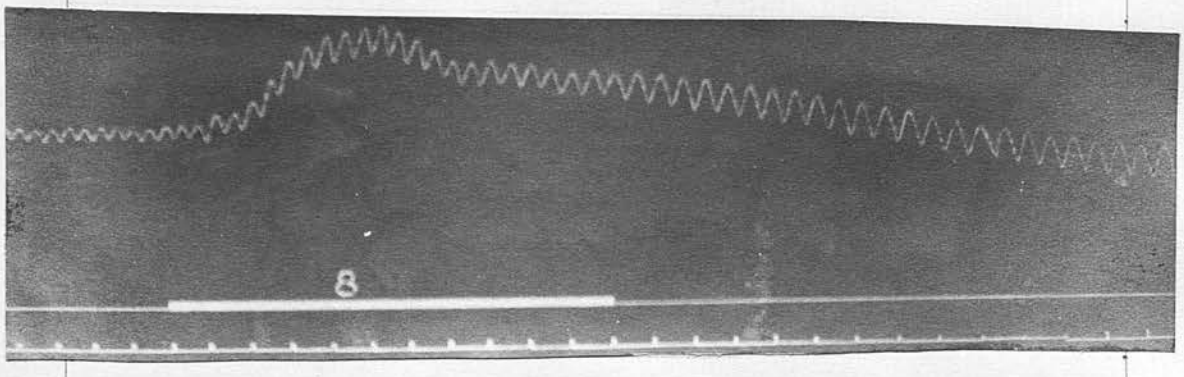

Fig. XXV C.

Fig. XXV. Effect of central vagal stimulation when heart slowed by weak peripheral vagal stimulation. Central Vagal Stimulus 8 cm.

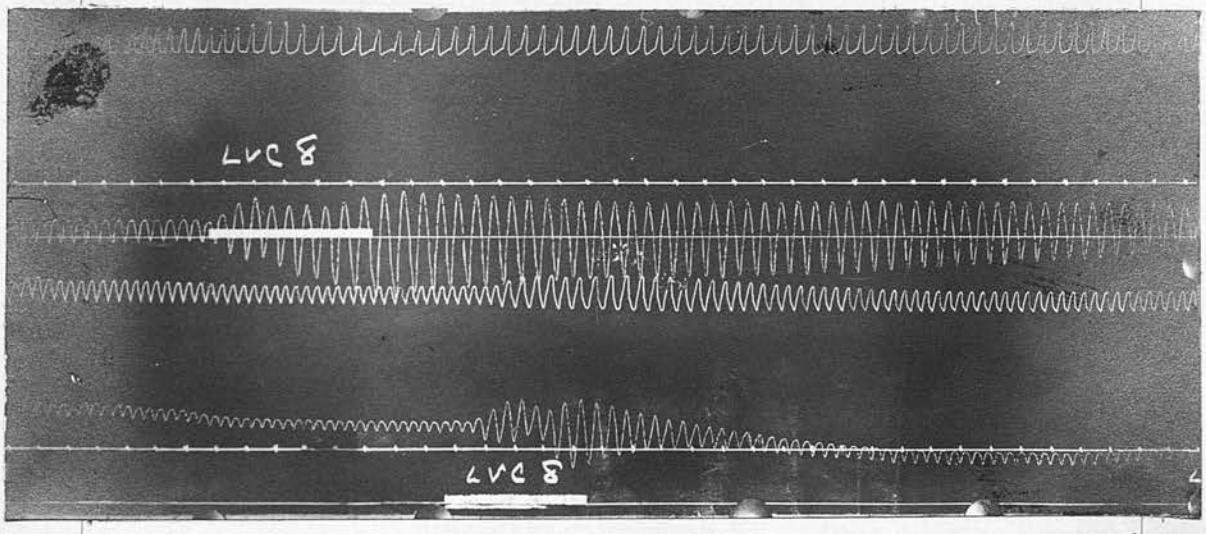

Fig. XXVI. Effect of central vagal stimulation when heart slowed by intravenous injection of Quinine Hydrochloride. Vagal stimulus = 8 cm. Lower tracing = Normal. Upper = During slowing.

DISCUSSION OF EXPERIMENTAL RESULTS.

The results shown in Table XIV show fairly conclusively that, afferent stimuli from parts other than the heart being excluded as far as possible, when the heart is beating more rapidly the same central vagal stimulation produces a greater effect than when it is beating at the normal rate. Also that when it is beating slowly the same stimulus produces a less marked effect than when the rate is normal.

It may be said that the effect is really due to alterations in arterial pressure with consequent alteration in the tonicity of the centre. In these experiments however there was usually no alteration in arterial pressure and when any did occur it was so small that it could play only an extremely small part in the results obtained. The view is therefore put forward that the impulses which influence the tonicity of the centre are afferent impulses in the vagi passing from the heart and great vessels.

It may be argued that the methods used to produce alterations in rate were liable to lead to fallacious results. Method I was only used in a few experiments as it was found that the rapid weakening of the heart which took place under the influence of these drugs and the accompanying rapid fall in blood pressure/

pressure necessitated a very rapid execution of the stimulation before the fall in arterial pressure had taken place to complicate the experiment. Another factor was that no return to normal took place.
It may be argued that in this method the drug damages the nervous mechanism. Although there is still considerable difference of opinion among pharmacologists as to whether these drugs have any action on the nervous apparatus of the heart Santesson[81] has brought forward strong evidence to show that Quinine slows the isolated frog's heart by direct action on the muscle. In the present series no difference could be found in the effect of peripheral vagal stimulation before and after the administration of the drugs so that any change which may occur must be in the centre itself. Only two experiments by this method are included in the series.

Regarding Method II it may be said that what is shown is really that a vagal stimulation is more effective when heat is applied to the sino-auricular node and less when cold is applied. As already stated there is a considerable diversity of opinion among physiologists as to what changes if any occur when heat or cold is applied to the S.A. node.
Stewart[73] found in the isolated frog's heart that inhibition/

inhibition was more difficult to produce when the heart was cooled but lasted longer, while heating the heart produced the opposite effect. In the tortoise's heart he found that there was a considerable margin above and below normal between which no change could be shown and that even at higher and lower temperatures it was difficult to show a definite change. The only experiments I know of in which this was investigated in carnivorae are those of Baxt[8] who working with dogs could produce no alteration in the effect of vagal stimulation by applying heat or cold to the node. In the present series no alteration of effect from normal was observed when the peripheral vagus was stimulated during the application of heat or cold to the node.

The objection which might be raised to Method III is that one is acting at the same point with both the means of producing the alteration in rate and the means of estimating the tonicity of the centre. It has been shown by Hunt[40] that, when the accelerators and vagus are stimulated together, the result is the algebraic sum of the result of separate stimulation. According to these results one would imagine when the accelerators were in opposition to the reflex vagal stimulation that the effect would be much less than when/

when the latter was superimposed on the peripheral vagal stimulation. The results show however that such is not the case and this seems to lend strong support to the view that the tonicity of the cardio-inhibitory centre varies with the heart rate.

GENERAL DISCUSSION OF RESULTS.

From the above results it is seen that the age incidence of maximum vagal activity is from 10 - 40 and that after 50 there is a considerable diminution of this activity. In Chronic Heart Disease there is also considerable reduction in the reaction obtained after atropine except in Auricular Fibrillation where the results are much higher than in other heart conditions. Cases of Exophthalmic Goitre show a lessened reaction while Parenchymatous Goitre shows a normal reaction. In cases of Typhoid Fever and during convalescence from Pneumonia the reaction is considerably reduced, but in Rheumatic Fever and Chorea there is a greater reaction than normal.

The reactions obtained in cases of Auricular Fibrillation under Digitalis show that stimulation of the inhibitory mechanism, although not wholly responsible, at least plays a part in the action of digitalis in this condition.

One sees that the original rate of the heart does not enable us to foretell what the reaction will be. In cases of heart disease the presence of signs of failure/

failure of the circulation, such as marked cyanosis or oedema, does not help us in judging what reaction will be obtained as many of the cases with these signs present gave as good and in some cases a better reaction than the average of those in which these signs were not present.

It may be said that in those cases in which the reaction was slight that atropine failed to paralyse the vagal terminations in the usual manner. This seems to me very unlikely as all the other symptoms due to atropine administration were present. It may also be argued that in the cases in which a slight reaction was obtained that really there was an increase in vagal tone which the dose of atropine administered failed to overcome. It is however almost inconceivable that in old age when all vital functions are on the wane that a sensitive mechanism like the inhibitory mechanism should increase its activity. It may be said that in all my cases the dosage was not sufficient to paralyse completely the vagal terminations and thus fallacious results were obtained. Muller[64] found that there was no appreciable difference between doses of 1 mg. and 2 mg. in his cases in which both were given. Cushny, Marris and Silberberg[16] also found little difference between $\frac{1}{50}$ gr. and $\frac{1}{25}$ gr. Marris in his/

his work on Typhoid Fever[57] found that $\frac{1}{33}$ gr. gave consistent results and also quotes a case where a second injection a short time after the first produced no increase. Recently Lewis[52] has stated that considerably greater doses require to be given to produce complete paralysis of the vagal terminations in the heart. In the cases in which an intravenous injection, which is the method Lewis advocates, follows a previous subcutaneous injection Lewis' charts show that the increased reaction is comparatively trivial. As it comes on immediately and only lasts a very short time it might conceivably be due to the prick of the needle and other factors connected with administration rather than to the further action of atropine. In the cases in which a large intravenous dose was given without previous subcutaneous injection the result seems to be greater. It is probable that the sudden flooding of the system with atropine produces a much greater disturbance than when it is gradually absorbed. This sudden flooding does not appear to produce the same marked reaction when atropine has been gradually absorbed previously. Lewis' cases were all cases of Auricular Fibrillation and he himself has shown that the intravenous administration of atropine produces marked alteration in the conduction and refractory period of the auricular muscle with a consequent marked/

marked fall in the auricular rate in this condition. This fall in auricular rate may allow more impulses to pass from the auricle to the ventricle, and this may prove to be the explanation of the diverse results obtained by Lewis and other observers. In any case as these are comparative results it does not seem to affect the main issue whether there may be some small part of vagal activity which is not abolished.

The question which now arises is how can these varied results be correlated. There appear to be three possible explanations.-

(1) That in cases where the reaction is low the vagus centre is acting weakly from deficient blood supply or from toxic influences and that in cases where there is an increased reaction the centre is stimulated by toxins. It is conceivable that if the various differences only took place after diseases known to be of toxic origin, that this might be the explanation. In old age lessened blood supply to the centre undoubtedly plays some part but in young people with bad hearts and no failure of circulation the typical result is obtained. No evidence was obtained of any difference in the systemic blood pressure between the cases with a low reaction and those with a normal/

normal reaction. The fact that in those cases with an altered reaction marked changes are found in the structure or function of the heart itself leads one to think that the primary cause of the disturbance is more likely to be there.

(2) That in a lessened reaction the intrinsic rhythm of the heart is slowed and consequently the normal number of afferent impulses do not pass to the centre to maintain it in its normal state of tone. In cases where the increased reaction takes place that the intrinsic rhythm is increased and more afferent impulses pass to the centre and increase its tonicity so that it may keep the heart rate within normal limits. Evidence has already been brought forward in one section of the present series of observations that the tonicity of the cardio-inhibitory centre can be altered by afferent impulses from the heart itself. This explanation is very fascinating and helps to explain many of the results obtained. In Typhoid Fever and after Pneumonia the pathological changes in the muscle cells themselves are of such a nature as to suggest that their normal functioning will be rendered much more sluggish and thus fewer afferent impulses would be produced. In fact a slow pulse during Typhoid/

Typhoid and after Pneumonia is often a marked feature. In Rheumatic Fever we have a different picture. Before sclerosis sets in there is usually no definite lesion of the muscle cells but an accumulation of cells - Aschoff's bodies - in the region of the small vessels. This type of lesion suggests irritability and it is well known that an irritable heart is the clinical picture during convalescence from Rheumatic Fever. The result of this irritability would be to increase the impulses to the centre, increasing its tonicity and thus produce an increased reaction to atropine administration. In Exophthalmic Goitre and Auricular Fibrillation the marked increase in rate sends more impulses to the centre and increases its tonicity, thus giving a well marked reaction. The reason why the heart is not maintained within normal limits and thus an even greater reaction obtained is due to the fact that the centre although doing its utmost is only able to counteract the powerful influences producing the tachycardia up to a certain point. The only cases which do not seem to fit into this explanation are cases of Chronic Heart Disease excluding Auricular Fibrillation. It is known that the heart in these conditions is in an irritable rather/

rather than a sluggish state so that one would expect the tonicity to be increased. It might be said that the tonicity was increased and that, although the centre was doing its best, much of its activity was lost dealing with impulses tending to quicken the heart. However Fig. XI shows that the heart deprived of vagal control, after which it ought to beat at its maximum rate, does not in these conditions attain to a rate much above normal, and not nearly to the height obtained in Auricular Fibrillation where a good reaction is obtained. One thus sees that although this explanation helps to correlate many of the reactions it fails to do so in others.

(3) That in cases with a lessened reaction the vagal terminations in the heart are rendered less active either from the effect of the general cardiac sclerosis on them in old age and in chronic heart disease, or from the toxins in fevers and consequently that the heart is under reduced nervous control, while in cases where the reaction is increased the vagal terminations are stimulated either by toxins or the type of pathological lesion in the heart.

This explanation would account very well for the lessened reactions observed in Chronic Heart Disease,/

Disease, Old Age, Typhoid Fever and after Pneumonia. It might be said that the general sclerotic changes in Heart Disease and the toxins in these febrile conditions had so affected the terminations that they were unable to convey to the muscle the impulses which they received from the centre. In Rheumatic Fever it might be said that the cell accumulations irritated the vagal terminations. However when we study Auricular Fibrillation it is difficult to show that this explanation accounts for the reactions. In Auricular Fibrillation the myocardium is known to be in a very badly damaged state and yet a considerable increase in rate is obtained after atropine so that it must still be possible to have a good deal of vagus control. The fall in auricular rate due to the atropine effect on the auricular muscle and consequent greater number of impulses being able to pass to the ventricle does not seem to be of sufficient extent to account for the marked reaction obtained. In Exophthalmic Goitre it is possible that the lessened reaction which is not so marked as in the other conditions may be due to slight impairment of function of the vagal terminations due to the exhausting effect on the heart of the prolonged tachycardia. However it seems unlikely when the heart is beating at this abnormal rate that if the inhibitory/

inhibitory mechanism is only slightly damaged the vagus centre continues to send out the usual number of impulses and does nothing to endeavour to control the abnormal rate.

From the preceding discussion one sees that no one explanation fully accounts for the facts. It is suggested that the factors mentioned in the second and third explanations are both at work. The following is an explanation of the results along these lines.

In Old Age and Chronic Heart Disease excluding Auricular Fibrillation the function of many of the vagal terminations in the heart is interfered with by the sclerotic changes and thus the vagus cannot produce its full effect either in conveying afferent or efferent impulses. As the centre receives fewer afferent impulses the slightly stronger impulses, which did pass, due to the rather greater irritability of the heart would to a large extent be used up in maintaining the central tone. The latter would not be increased sufficiently to send out strong enough impulses to make up for the lessened number which can affect the cardiac muscle. In Auricular Fibrillation on the other hand the heart rate is so rapid and the heart so irritable that impulses are showered on the centre by the fibres which have not been put out

of/

of action. The centre is aroused to a state of unwonted activity so that much stronger impulses are sent along the intact fibres and provide a considerable amount of brake. The same explanation is applicable to Exophthalmic Goitre. The centre is not able despite its efforts to keep the original rate within normal limits as such powerful influences are opposed to it. In Auricular Fibrillation the reduction of Auricular beats after atropine administration from the effect on the muscle doubtless accounts for a certain amount of the large reaction obtained but does not seem to be sufficient to account for it all.

In Typhoid Fever and after Pneumonia the heart is in a torpid state and the vagal terminations are damaged by the toxins. There are thus fewer afferent impulses and the central tone is lowered. The efferent impulses which are sent out by the centre have also greater difficulty in affecting the muscle. In Rheumatic Fever on the other hand the cellular accumulations stimulate the efferent fibres thus increasing their action and also the afferent fibres thus increasing central tone.

C O N C L U S I O N S.

(1) The age incidence of maximum vagal activity in normal persons is from 10 - 40 years, being at its height from 20 - 30. After this it steadily begins to decline there being a marked fall after 50.

(2) The increase in heart rate after atropine administration cannot be foretold from the heart rate before injection.

(3) In the normal heart when afferent impulses from other parts of the body are excluded as far as possible an increase of heart rate increases the tonicity of the cardio-inhibitory centre while a slowing of rate lessens the tonicity. It is suggested that this is due to afferent impulses passing from the heart and great vessels through the vagi.

(4) There is diminished vagal control in all cases of Chronic Heart Disease, especially in Aortic Disease and Mitral Stenosis. In Auricular Fibrillation the reaction under atropine is about normal. Part of this reaction is due to the action/

action of atropine on the auricular muscle causing a reduction in rate and thus enabling more impulses to pass to the ventricle. When this factor is deducted there is probably a slight loss of control also in this condition although much less than in the other heart conditions. Typhoid Fever and Pneumonia during convalescence show diminished control and Exophthalmic Goitre shows the same to a less extent.

(5) In Rheumatic Fever and Chorea the vagal control of the heart is increased.

(6) It is suggested that the varied results obtained are due to two factors (a) alteration of the tonicity of the cardio-inhibitory centre, (b) changes in the vagal terminations in the heart itself.

(7) The action of Digitalis in Auricular Fibrillation is partly due to direct action on the muscle and partly to stimulation of the inhibitory mechanism.

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